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A population pharmacokinetic analysis of fimasartan, a novel angiotensin-receptor antagonist, in healthy subjects and patients with hypertension

건강 자원자와 고혈압 환자에서 fimasartan 의 집단 약동학 연구

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서울대학교 융합과학기술대학원

융합과학부 방사선융합의생명 전공

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이 희 찬의 의학석사 학위논문을 인준함

2017년 6월

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Abstract

A population pharmacokinetic analysis of fimasartan, a novel angiotensin-receptor antagonist, in healthy subjects and patients with hypertension

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Introduction: Fimasartan is a newly developed antihypertensive agent that selectively blocks the type 1 angiotensin II receptor. The objectives of this study were

to develop a population pharmacokinetic (PK) model of fimasartan and to identify significant covariates that may affect the population PK parameters in healthy subjects and patients with hypertension.

Method: A total of 3,978 fimasartan plasma concentrations were obtained from 268 subjects enrolled in 11 clinical trials including a first-in-human study, drug-interaction studies, and a proof-of-concept dose-response study. A population PK model was developed using nonlinear mixed-effects modeling analysis methods implemented in NONMEM (ver. 7.40). The iterative-two stage, Stochastic Approximation Expectation-Maximization and Monte-Carlo Importance Sampling assisted by mode a posteriori estimation with mu-referencing were implemented, which was followed by model qualification using goodness of fit plots and visual predictive checks (VPCs).

Results: A two-compartment linear model with mixed absorption (zero- + first-order), lag time and first-order elimination adequately described plasma fimasartan concentration. A proportional error models were used to account for remained intra-subject variability. The typical values of population PK parameters (inter-individual variability, CV%) of apparent clearance, apparent central volume of distribution, and fraction absorbed via first-order process was 159 L/h (53.7%), 371 L (71.8%), and 0.367 (114.6%). Covariates such as body weight and age were included in the model. Model evaluation by goodness of fit plots and VPCs suggested that the proposed model was adequate and robust with good precision.

Discussion: The final population PK model adequately described the observed plasma concentration of fimasartan in various population groups. Body weight and hepatic impairment status were selected as significant covariate of the final population PK model for fimasartan.

Keywords: Population pharmacokinetic (PK) model; NONMEM; Covariate; Fimasartan

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List of abbreviations and symbols

PK	Pharmacokinetic
OFV	Objective function value
VPC	Visual predictive check
IIV	Inter-individual variability
IOV	Inter-occasional variability
IBW	Ideal body weight
BMI	Body mass index
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
GFR	Glomerular filtration rate
CL/F	Apparent oral clearance
V_c/F	Apparent volume of central compartment
Q/F	Apparent intercompartmental clearance
V_p/F	Apparent volume of peripheral compartment
Ka	Absorption rate constant
F1	Proportionality constant for fraction of zero-order absorption process

D2	Virtual duration of dosing for zero order absorption
Lag1	Lag time for first-order absorption

Introduction

Hypertension is a disease that systemic arterial pressure is chronically evaluated above the threshold for the diagnosis of hypertension, which are a systolic blood pressure or a diastolic blood pressure measured in a clinic or office ≥ 140 mm Hg or ≥ 90 mm Hg, respectively, or both.[1,2] Hypertension is considered not only as a major factor for cardiovascular and kidney diseases and but also as the biggest single contributor to the global burden of disease and to global mortality by the Global Burden of Disease project.[2,3] Furthermore, the number of patients with hypertension in worldwide is predicted to increase to about 1.56 billion people by 2025.[2,4] As a result, many drugs and treatment methods were developed to control blood pressure and treat hypertension.

Angiotensin II receptor blockers (ARBs), one class of antihypertensive drug, reduce blood pressure of hypertension patients by binding angiotensin II AT1 receptor and protecting angiotensin II mediated responses.[5] ARB is proved to be highly effective blood-pressure-lowering agent, which suggested that ARB is used as first-line therapy or combination therapy with other antihypertensive for the management of hypertension based on the Eighth Joint National Committee (JNC 8).[5,6]

Fimasartan (BR-A-657), chemically 2-((2-butyl-4-methyl-6-oxo-1-([20-(1H-tetrazol-5-yl)biphenyl- 4-yl] methyl)-1,6-dihydropyrimidine-5-yl))-N,N-dimethylthioacetamide, is a novel non-peptide ARB with a selective type I receptor

blocking effect approved for use in hypertension patient in September 2010 in Republic of Korea (figure 1).[7] Fimasartan is rapidly absorbed with a time to peak plasma concentration (t_{max}) ranging from 0.5 to 4 hours in healthy subjects and with second peak in concentration profile of fimasartan. Dose proportionality for the peak plasma concentration (C_{max}) and the area under the plasma concentration–time curve (AUC) of fimasartan was identified ranging from 20 mg to 480 mg.[8] Fimasartan is eliminated with a half-life ranging 9 to 16 hours through mainly non-renal elimination pathway such as bile elimination or metabolism.[8,9] Furthermore, fimasartan reduced blood pressure in patient with mild to moderate hypertension and its effect is comparable to or slightly better than the same class drugs such as losartan[10] and valsartan.[11]

Recently, population PK analysis has been applied to new drug development for a variety hypertension drugs.[12-14] The population PK analysis can quantify not only the typical values of PK parameters but also their variability among subjects. Additionally, population PK analysis can evaluate the influence of covariates to explain the variability between different individuals. The previous study developed the population PK model of fimasartan and evaluate the covariates' effects using population-based pharmacokinetic analysis in healthy Caucasian subjects and Korean patients with hypertension, while the study did only use data from the three clinical trials.[15] However, since the previous study was published, many clinical studies for fimasartan have been conducted in a variety of population and clinical setting such as food effect study and drug-drug interaction study. Therefore, to better understand PK

characteristics of fimasartan, this study decide to develop a population PK model for fimasartan using rich data of various clinical trial settings.

We developed a population PK model of fimasartan and evaluated effects of the selected covariates on the PK parameters of fimasartan in healthy subjects, patients with mild to moderate hypertension and special population groups.

Methods

Clinical Trials and Subjects

This study used fimasartan plasma time-dependent concentrations obtained from 269 subjects enrolled in 11 clinical trials including a first-in-human study, drug-interaction studies, and a proof-of-concept dose-response study, food effect study, special population studies, drug-interaction study. However, the fimasartan plasma concentrations from subjects with co-administration of concomitant drugs (ketoconazole, rifampicin, amlodipine, and hydrochlorothiazide) were excluded because the development of a population PK model of fimasartan itself is prioritized before assessing effects of concomitant drugs on exposure of fimasartan. Furthermore, the pre-dose concentration of one subject in study 4 was very high comparted to the mean pre-dose concentration of the other subject in study 4 (about 46 times higher), which supported that all concentrations (3 concentrations) for the subject in the study 4 were excluded from our dataset. Therefore, this study used a total of 3,698 fimasartan plasma time-dependent concentrations obtained from 268 subjects (Table 1).

Table 1. Summary of the eleven clinical trials

	Study 1	Study 2	Study 3	Study 4
Number of subjects	30 (Healthy subjects)	12 (Healthy subjects)	27 (Patients)	59 (Patients)
Study characteristic	First-in-human	First-in-human	Proof-of-concept dose-response study	Proof-of-concept dose-response study
Drug administration	Single dose 20, 60, 120, 240*, 480 mg under fasting state (*:under fasting and fed state)	7 days multiple dose 120, 360 mg under fasting state	4 weeks multiple dose 20, 60, 180 mg	8 weeks multiple dose 60, 120 mg
Blood sampling points	0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, and 48 h post-dose	at 0, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36*, and 48* h post-dose on Days 1 and 7 under fasting state (*: Day 7 only)	pre-dose (0 h), 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48 (Day 28 only) h post-dose on Day 1 and 28 pre-dose (0 h) on Day 8, 15, 22	pre-dose (0 h), 3, 8 h post-dose on Day 29
Bioanalytic institute	The United Kingdom	The United Kingdom	The South Korea	The South Korea
Lower limit of quantification	0.4 ng/mL	0.4 ng/mL	0.2 ng/mL	0.5 ng/mL
ClinicalTrial.gov identifier	NCT01289886	NCT01289899	NCT00937651	NCT00922441

Table 1. Summary of the eleven clinical trials.

	Study 5	Study 6	Study 7	Study 8
Number of subjects	23 (Healthy subjects)	18 (Healthy subjects)	19 (Healthy subjects)	24 (Healthy subjects)
Study characteristic	Drug interaction study (ketoconazole, Rifampicin)	Drug interaction study (Hydrochlorothiazide)	Drug interaction study (Amlodipine)	Food effect study
Drug administration	Single dose 240 mg under fasting state	Multiple dose 240 mg under fasting state	Multiple dose 120 mg under fasting state	Single dose 240 mg under fasting and fed state
Blood sampling points	pre-dose (0 h), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 32, 48* and 56* h post-dose (*: period 2 only)	pre-dose (0 h), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 h post-dose on Day 7 and 21	pre-dose (0 h), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 h post-dose on Days 7 and 21 under fasting state	pre-dose (0 h), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 h post-dose on Day 7 and 21 under fasting and fed state
Bioanalytic institute	The South Korea	The South Korea	The South Korea	The South Korea
Lower limit of quantification	0.5 ng/mL	0.5 ng/mL	0.5 ng/mL	0.5 ng/mL
ClinicalTrial.gov identifier	NCT00938262	NCT00923533.	NCT00938197	NCT00923533

Table 1. Summary of the eleven clinical trials.

	Study 9	Study 10	Study 11
Number of subjects	8 (Healthy subjects) 8 (Renal impairment subjects)	6 (Healthy subjects) 12 (Hepatic impairment subjects)	12 (Young subjects, 19-45 years) 10 (Elderly subjects, > 65 years)
Study characteristic	Special population study	Special population study	Special population study
Drug administration	Single dose 120 mg under fasting state	Single dose 120 mg under fasting state	Single dose 240 mg under fasting state
Blood sampling points	pre-dose (0 h), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 32 and 48 h post-dose under fasting state	pre-dose (0 h), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 32, and 48 h post-dose under fasting state	pre-dose (0 h), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24 and 48 h post-dose under fasting state
Bioanalytic institute	The South Korea	The South Korea	The South Korea
Lower limit of quantification	0.5 ng/mL	0.5 ng/mL	0.5 ng/mL
ClinicalTrial.gov identifier	NCT01148368	NCT01146938	NCT00937534

Population pharmacokinetic analysis

A population PK model was developed using nonlinear mixed-effects modeling analysis methods implemented in NONMEM (version 7.40, Icon Development Solution, Ellicott City, MD USA). The iterative-two stage, Stochastic Approximation Expectation-Maximization and Monte-Carlo Importance Sampling assisted by mode a posteriori estimation with mu-referencing were implemented in the model. Model appropriateness was evaluated by evaluation of the change in the objective function value (OFV) produced by the addition of model parameters. Furthermore, Goodness-of-fit plots and standard errors on each model parameter estimate were used as an additional check of model appropriateness. The model was validated by visual predictive checks (VPCs).

Population pharmacokinetic model development

The individual plasma concentration profiles and the mean plasma concentration profile of fimasartan was plotted to investigate PK characteristic of fimasartan and variability in the data by using graphical analysis (Figure 1, 2, 3, 4, 5, and 6). One-, two- and three-compartment disposition models with zero-, first- and mixed (zero- + first-) order absorption and first-order elimination were evaluated.

Inter-individual variability (IIV) and inter-occasional variability (IOV) was assessed on all structural model parameters using exponential random effects models.

$\theta_{ij} = \exp(\theta_{TV} + (\eta_i) + (\kappa_{ij}))$

where θ_{ij} is the individual lognormal value of the parameter at sampling occasion j (e.g., apparent clearance or volume of distribution), θ_{TV} is the typical value model parameter in the population, η_i denotes the inter-individual random effect accounting for the ith individual's deviation from the typical value, assumed to have a normal distribution with a zero mean and variance ω^2, and κ_{ij} is the IOV, assumed to have a normal distribution with mean zero and variance π^2.

Residual variability was modeled using combined proportional and additive random effect models.

$y_{ij} = \hat{y}_j \cdot \exp(\varepsilon_1) + \varepsilon_2$

where y_{ij} is the observation in individual i at sampling time j, $\hat{y}_j$ is the typical population prediction at sampling time j, ε_1 is an exponential residual error term, and ε_2 is an additive residual error term.

The effects of covariates (age, weight, height, ideal body weight (IBW), body mass index (BMI), albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphate, glomerular filtration rate (GFR), gender, race, hypertension disease status, food intake status, renal impairment status, hepatic impairment status) on the pharmacokinetic parameters of fimasartan were investigated. The covariates were entered into the model using physiological relevance, forward selection or backward elimination step after a structural model

and stochastic model for fimasartan PK had been developed. Among them, physiological was considered as the most important factor. In forward selection step, a covariate was retained in the model if OFV was reduce more than 3.84 ($\alpha = 0.05$ for 1 degree of freedom), while, in backward elimination step, a covariate was retained in the model if OFV was increased more than 10.83 ($\alpha = 0.01$ for degree of freedom).

For continuous covariates, relationships were tested as using a power model; age, weight, height, IBW, BMI, albumin, total bilirubin, alkaline phosphate, AST, ALT, GFR,

$$P_i = \theta_0 \cdot [X_{ij} / M(X_j)]^{\theta_j}$$

where P_i is the value of parameter P for individual i, θ_0 is the typical value of P with no covariate effect, θ is term that relates the covariate to the typical value θ_0, Xi is the covariate value of individual i, and M(X) is the median of covariate X.

For dichotomous covariates, relationships were tested as using a fractional change to the typical value; gender, hypertension disease status, renal impairment status, hepatic impairment status

$$P_i = \theta_0 \cdot (\theta_i)^X$$

where P_i is the value of parameter P for individual i, θ_0 is the typical value of P with no covariate effect, X is either 0 or 1 (0 = without covariate X and 1 = with covariate X).

For categorical covariates, relationships were tested as using a fractional change to the typical value; race, food intake status

$P_i = \theta_0 \cdot (\theta_x)$

where P_i is the value of parameter P for individual i, θ_0 is the typical value of P with no covariate effect (X is 0), X is either 0, 1 or 2; 1) 0 = Korean, 1 = Cuacasian, 2 = other races in race covariate, 2) 0 = fasting state, 1 = fed state for subject administered to 240 mg in first-in human study (study 1), 2 = fed state for subjects in food effect study (study 8) in food intake status covariate.

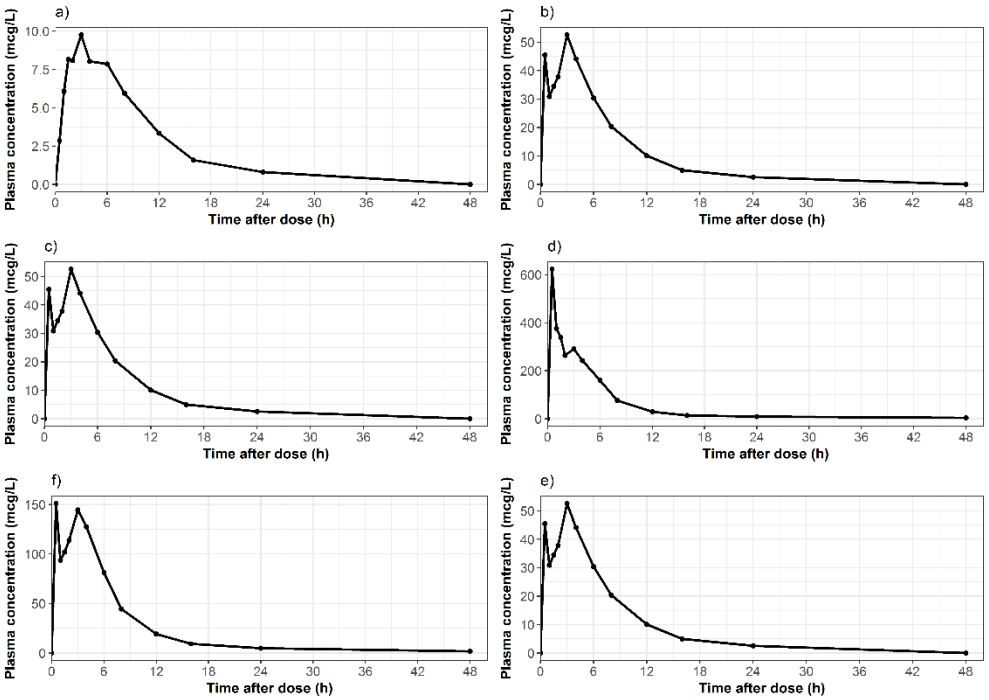


Figure 1 Mean observed plasma concentration-time curves of fimasartan; a) 20 mg in study 1, b) 60 mg in study 1, c) 120 mg in study 1, d) 480 mg in study 1, e) 240 mg under fasting state in study 1, f) 240 mg under fed state in study 1

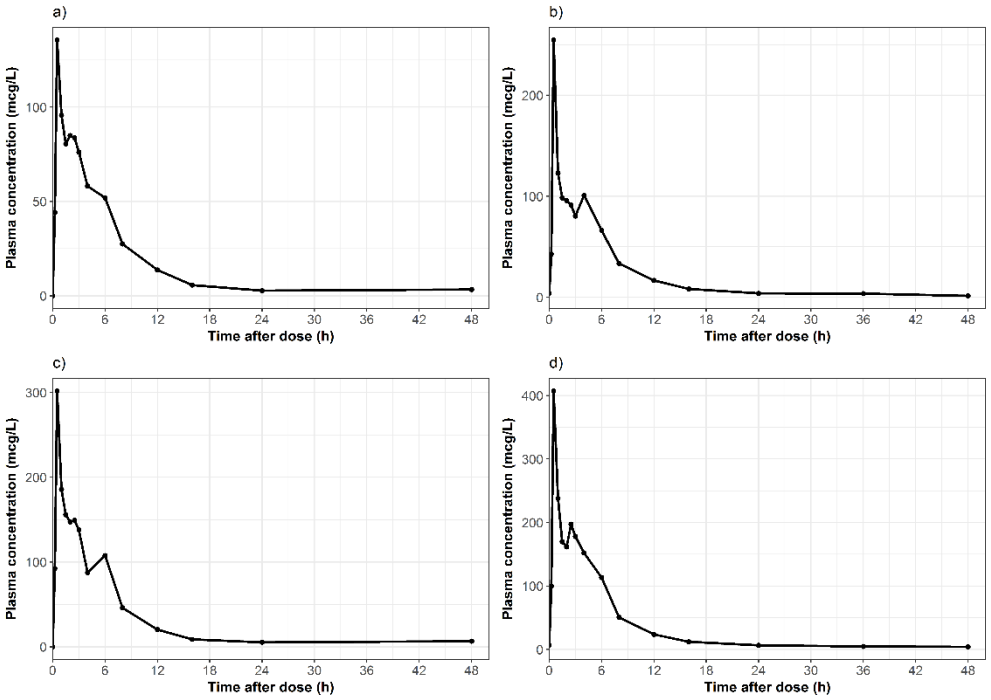


Figure 2 Mean observed plasma concentration-time curves of fimasartan; a) 120 mg at day 1 in study 2, b) 120 mg at day 7 in study 2, c) 360 mg at day 1 in study 2, d) 360mg at day 7 in study 2

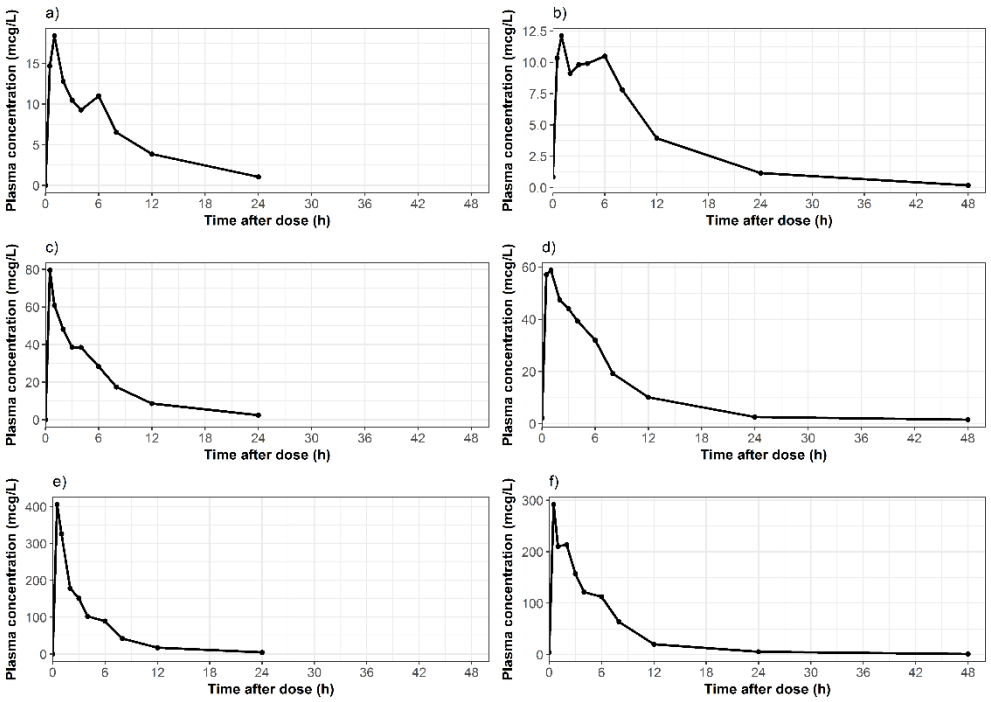


Figure 3 Mean observed plasma concentration-time curves of fimasartan; a) 20 mg at day 1 in study 3, b) 20 mg at day 28 in study 3, c) 60 mg at day 1 in study 3, d) 60 mg at day 28 in study 3, e) 180 mg at day 1 in study 3, f) 180 mg at day 28 in study 3

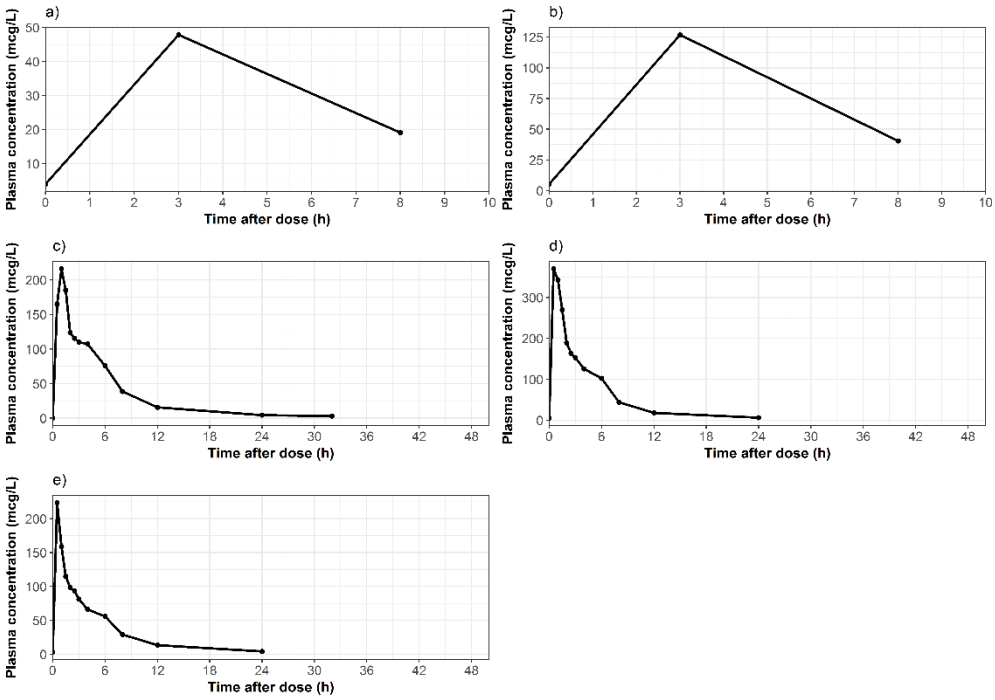


Figure 4 Mean observed plasma concentration-time curves of fimasartan; a) 60 mg in study 4, b) 120 mg in study 4, c) 240 mg in study 5, d) 240mg in study 6, e) 120 mg in study 7

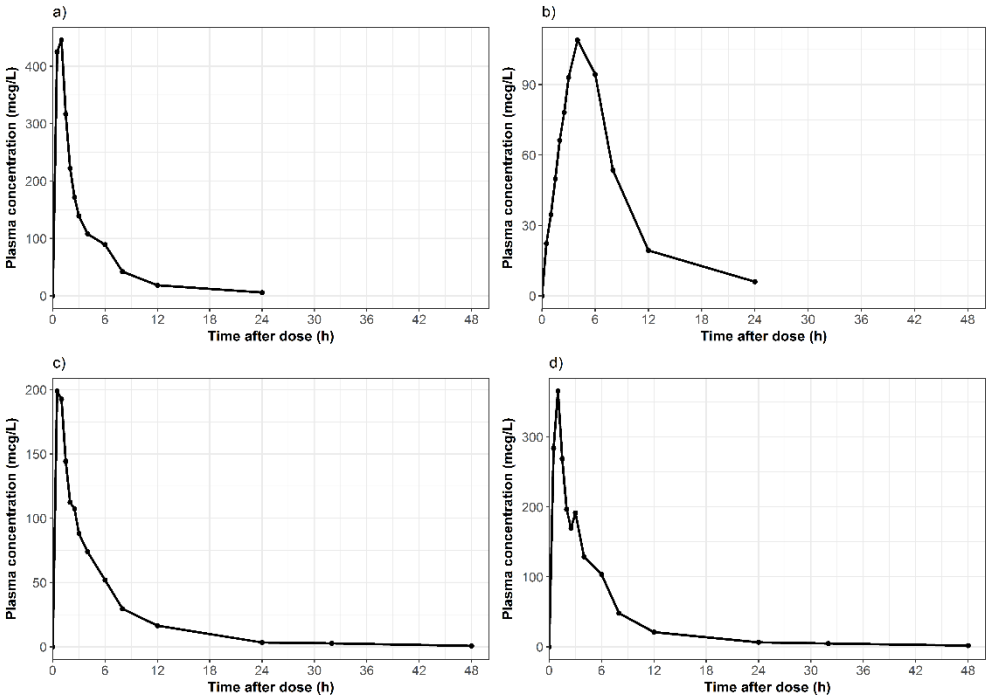


Figure 5 Mean observed plasma concentration-time curves of fimasartan; a) 240 mg under fasting state in study 8, b) 240 mg under fed state in study 8, c) 120 mg of health subjects in study 9, d) 120mg of severe renal impairment subjects in study 9

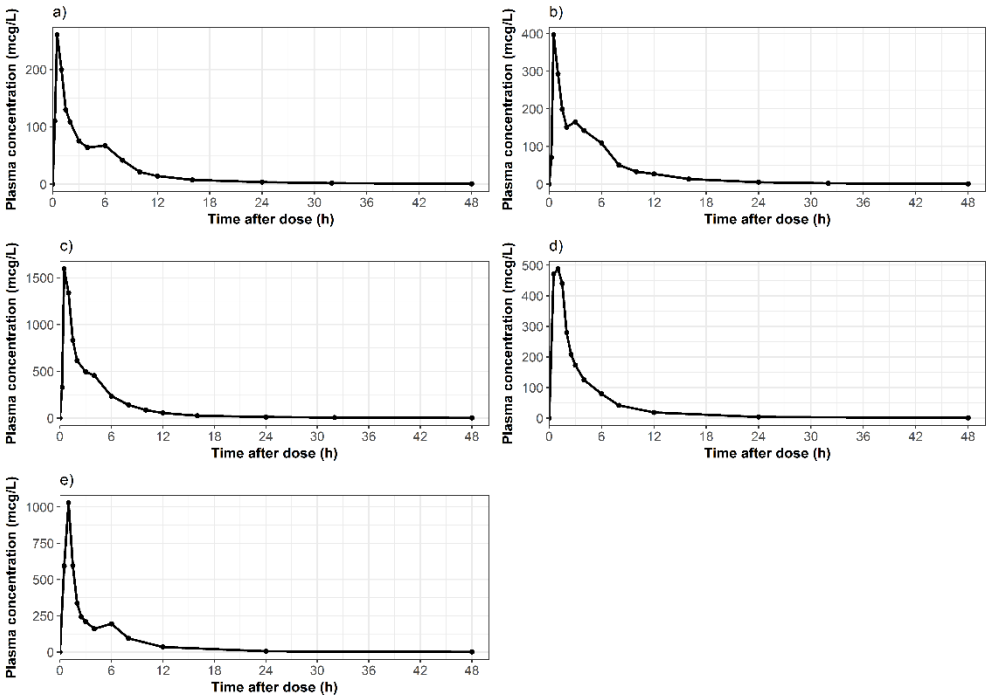


Figure 6 Mean observed plasma concentration-time curves of fimasartan; a) 120 mg of healthy subjects in study 10, b) 120 mg of mild hepatic impairment subjects in study 10, c) 120 mg of moderate hepatic impairment subjects in study 10, d) 240 mg of young subjects in study 11, e) 240 mg of elderly subjects in study 11

Population pharmacokinetic model evaluation

Goodness-of-fit plots and the visual predictive check (VPC) was used to assess the predictive performance of the final model. VPC was obtained from 1000 simulated replicates of original data using the Perl-Speaks-NONMEM software, and then whether original data were adequately included in 90 % interpercentile range (upper 95^{th} and lower 5^{th} percentiles) of VPC was evaluated.

Result

Demographic characteristic

The mean age, weight and BMI of the 268 subjects were 40.1 ± 14.5 years (range 19 – 74 years), 68.8 ± 9.8 kg (range 43.5 – 95.7 kg), and 23.8 ± 2.6 kg/m^2 (range 17.8 – 38.1 kg/m^2), respectively (Table 2). Most subjects were Korean (N = 226) and other races (N = 42) were included in the study 1 and 2. Also, most subjects were male subjects (N = 233) and female subjects (N = 35) were only included in the study 3 and 4 (Table 2). Hypertension patients (N = 86) were included in the study 3 and 4 and Elderly subjects (≥ 65 years, N = 14) were included in study 4 and 11, respectively. Renal impairment subjects (N = 8) were included in study 9 and were all severe renal impairment subjects (estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease formulation lower than 30 mL/min/1.73 m^2), while Hepatic impairment subjects (N = 12) were included in study 10 and the subjects with mild hepatic impairment were 6 and the subjects with moderated hepatic impairment were 6, respectively.

Table 2. Demographic data for subjects in 11 clinical trials

	Study 1 (N=30)	Study 2 (N=12)	Study 3 (N=27)	Study 4 (N=59)	Study 5 (N=23)	Study 6 (N=18)
Age (years)	32.1 ± 10.4	32.5 ±10.6	51.7 ± 7.8	53.0 ± 8.6	30.3 ± 5.7	25.3 ± 4.4
Body weight (kg)	73.3 ± 10.3	79.2 ± 6.5	66.4 ± 12.0	68.1 ± 9.9	69.3 ± 7.8	67.8 ± 8.5
Height (cm)	175.1 ± 6.9	175.8 ± 7.4	162.7 ± 9.1	164.7 ± 7.8	174.0 ± 6.3	173.5 ± 5.7
Body mass index (kg/m^2)	24.6 ± 3.0	25.7 ± 1.5	24.9 ± 3.0	25.0 ± 2.8	22.8 ± 1.7	22.5 ± 2.1
Serum albumin (g/dL)	4.4 ± 0.3	4.3 ± 0.2	4.3 ± 0.2	4.6 ± 0.3	4.6 ± 0.2	4.6 ± 0.2
Total bilirubin (mg/dL)	0.7 ± 0.3	0.6 ± 0.3	1.2 ± 0.5	0.8 ± 0.3	0.9 ± 0.3	1.0 ± 0.5
Alkaline phosphatase (IU/L)	158.3 ± 35.8	172.8 ± 30.6	70.4 ± 19.0	127.4 ± 94.4	64.7 ±14.7	67.9 ± 18.8
AST (IU/L)	22.4 ± 5.7	22.3 ± 3.0	26.1 ± 8.4	26.8 ± 21.9	19.1 ± 4.3	19.4 ± 5.9
ALT (IU/L)	23.1 ± 8.6	21.4 ± 3.9	32.3 ± 19.9	30.7 ± 36.5	19.7 ± 8.6	19.8 ± 12.3
GFR (mL/min)	85.3 ± 11.7	85.9 ± 11.4	86.2 ± 13.9	69.2 ± 19.9	93.9 ± 15.5	88.4 ± 7.0
Male, no (%)	30 (100)	12 (100)	15 (55.6)	36 (61.0)	23 (100)	18 (100)
Race, no (%)						
Caucasian	29 (96.7)	11 (91.7)				
Korean	1 (3.3)		27 (100)	59 (100)	23 (100)	18 (100)
Other		1 (8.3)				

Table 2. Demographic data for subjects in 11 clinical trials

	Study 7 (N=19)	Study 8 (N=24)	Study 9 (N=16)	Study 10 (N=18)	Study 11 (N=22)	Total (N=268)
Age (years)	23.9 ± 1.7	30.6 ± 6.5	44.6 ± 8.7	46.7 ± 7.7	44.3 ± 23.0	40.1 ± 14.5
Body weight (kg)	66.6 ± 6.7	71.0 ± 9.8	58.5 ± 2.6	69.2 ± 7.0	65.7 ± 7.1	68.8 ± 9.8
Height (cm)	175.1 ± 5.2	176.3 ± 7.9	161.9 ± 5.7	171.1 ± 5.5	170.3 ± 6.7	170.0 ± 8.7
Body mass index (kg/m^2)	21.7 ± 1.7	22.8 ± 2.1	22.4 ± 1.7	23.6 ± 1.9	22.6 ± 1.6	23.8 ± 2.6
Serum albumin (g/dL)	4.7 ± 0.3	4.6 ± 0.2	4.1 ± 0.2	3.9 ± 0.7	4.8 ± 0.3	4.5 ± 0.4
Total bilirubin (mg/dL)	1.0 ± 0.5	0.9 ± 0.3	0.7 ± 1.9	1.7 ± 1.4	1.2 ± 0.3	0.9 ± 0.5
Alkaline phosphatase (IU/L)	71.4 ± 15.4	59.1 ± 13.2	51.7 ± 11.4	78.6 ± 37.4	79.0 ± 18.7	95.9 ± 61.6
AST (IU/L)	17.3 ± 4.2	18.8 ± 4.3	22.3 ± 9.9	32.6 ± 22.0	24.6 ± 3.7	23.4 ± 13.2
ALT (IU/L)	16.0 ± 5.8	20.3 ± 7.1	19.4 ± 14.2	28.3 ± 14.4	18.3 ± 5.8	24.1 ± 20.4
GFR (mL/min)	98.1 ± 13.6	107.8 ± 12.2	65.1 ± 45.0	105.3 ± 17.9	99.0 ± 13.5	87.0 ± 22.5
Male, no (%)	19 (100)	24 (100)	16 (100)	18 (100)	22 (100)	233 (86.9)
Race, no (%)						
Caucasian						40 (14.9)
Korean	19 (100)	24 (100)	16 (100)	18 (100)	22 (100)	227 (84.7)
Other						1 (0.4)

Population pharmacokinetic analysis

A two-compartment disposition, first-order elimination model with a proportional residual error was selected to describe plasma concentration profile of fimasartan based on individual and mean concentration profile of fimasartan (Figure 1, 2, 3, 4, 5, 6 and Appendices). The model included parameters: apparent clearance (CL/F, L/h), apparent central volume of distribution (V_c/F, L), apparent intercompartmental clearance (Q, L/h), apparent peripheral volume of distribution (V_p/F, L), absorption rate constant (ka, h^{-1}). The plasma concentration profiles of fimasartan in many subjects under fasting state showed the rapid absorption with faster T_{max} and the delayed second peak after administration of fimasartan, which supported that the mixed absorption model (zero- + first-absorption model) and lag-time were selected as the absorption model of fimasartan. Therefore, the model included additional parameters; the relative bioavailability of first-absorption (F1) and the relative bioavailability of zero-order absorption (F), assuming F1+F2=1, lag time (ALAG1, h^{-1}), duration of zero-order absorption (D2, h^{-1}) (Figure 7).

However, the concentration profile of fimasartan under fed state in study 8 showed the considerably delayed T_{max} and sigmoidal absorption pattern, which could adequately not be described by the mixed absorption model (Figure 5a, and b). Therefore, the absorption model of fimasartan under the fed state would be estimated

and hence, the Weibull absorption model was selected as the absorption model of fimasartan under the fed state (Figure 7).

Inter-individual variability (IIV) and inter-occasional variability (IOV) was assessed on all structural model parameters using exponential random effects models. IIV for all PK parameters in this model was contained because of the decreased OFV and the improvements in diagnostic plots. Furthermore, the OMEGA BLOCK structure among all IIVs improved model fit, and then was contained in the population PK model of fimasartan. The selected population PK model included IOV on CL/F, V_c/F, and D2 and then also included the OMEGA BLOCK structure among all IOVs (Table 3, Table 4 and Table 5).

In addition, covariate effects on the pharmacokinetic parameters of fimasartan were investigated based on the physiological relevance, the decreased OFV and improvement in diagnostic plots. Among the several covariate models, the following covariates was contained in population PK model; body weight for CL/F, V_c/F, Q/F, V_p/F, hepatic impairment status for CL/F. The PK parameters of the final model were summarized in Table 3, Table 4 and Table 5.

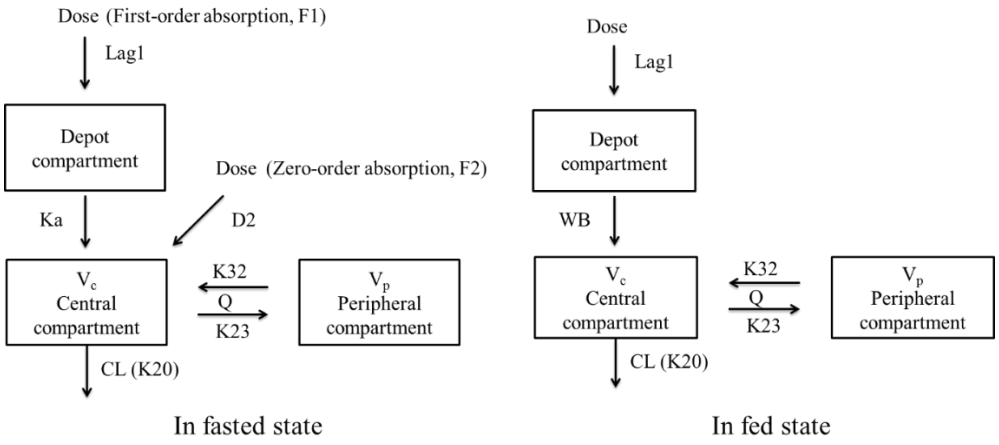


Figure 7 Population pharmacokinetic structure models for fimasartan; CL; Apparent oral clearance, Vc/; Apparent volume of central compartment, Q; Apparent intercompartmental clearance, Vp; Apparent volume of peripheral compartment, Ka; Absorption rate constant, F1; Proportionality constant for fraction of first-order absorption process, F2; Proportionality constant for fraction of zero-order absorption process, D2; Virtual duration of dosing for zero order absorption, Lag1; Lag time for first-order absorption, WB; Weibull constant

Table 3. Population pharmacokinetic parameter estimates of the final model for fimasartan

Parameter	Estimate (RSE)	IIV (CV%)	IOV (CV%)
CL/F; Apparent oral clearance (L/h)	159 (2.7%)	53.7	14.2
Θ15; Body weight on CL/F	0.435 (39.8%)		
Θ19; Hepatic impairment status on CL/F	0.362 (18.6%)		
V_c/F; Apparent volume of central compartment (L)	371 (4.3%)	71.8	40.8
Θ16; Body weight on V_c/F	0.76 (31.8%)		
Q/F; Apparent intercompartmental clearance (L/h)	39.5 (5.7%)	104.6	
Θ17; Body weight on Q/F	0.606 (56.8%)		
V_p/F; Apparent volume of peripheral compartment (L)	457 (5.9%)	101.4	
Θ18; Body weight on V_p/F	1.02 (27.5%)		
Ka; Absorption rate constant (h^{-1})	0.423 (5.4%)	43.3	
F1; Proportionality constant for fraction of first-order absorption process	0.367 (4.6%)	114.6	
D2; Virtual duration of dosing for zero order absorption (h)	0.778 (4.6%)	28.9	91.5
Lag1; Lag time for first-order absorption (h)	2.38 (1.4%)	14.2	
BA; Bioavailability of fed state when that of fasting state was assumed to be 1	0.627 (3.5%)	38.3	
Gamma; shape factor for absorption	7.29 (31.1%)	681.7	
Interindividual variability in residual error		40.1	
Proportional residual variability in Study 1 and 2 (CV%)	27.3 (15.5%)		
Proportional residual variability in Study 3, 4, 5, 6, 7, 8, 9, 10, and 11 (CV%)	26.1 (5.2%)		

$CL/F = 153 \times (\text{body weight}/70)^{\Theta 15} \times (\Theta 19)^{\text{hepatic impairment status}}$

$Vc/F = 319 \times (\text{body weight}/70)^{\Theta 16}$

$Q/F = 35.5 \times (\text{body weight}/70)^{\Theta 17}$

$Vp/F = 452 \times (\text{body weight}/70)^{\Theta 18}$

CV, coefficient of variation; IIV, inter-individual variability; IOV, inter-occasion variability; RSE, relative standard error.

Table 4. Correlation coefficient between inter-individual variability terms

	IIV of CL/F	IIV of V_c/F	IIV of Q/F	IIV of V_p/F	IIV of KA	IIV of F1	IIV of D2	IIV of ALAG1	IIV of BA	IIV of Gamma	IIV of error
IIV of CL/F	1										
IIV of V_c/F	0.274	1									
IIV of Q/F	0.328	0.51	1								
IIV of V_p/F	0.344	0.517	0.672	1							
IIV of KA	0.0385	0.116	0.121	0.114	1						
IIV of F1	0.286	0.482	0.462	0.518	0.24	1					
IIV of D2	0.0627	0.0989	0.135	0.13	0.0608	0.161	1				
IIV of ALAG1	-0.0371	-0.057	-0.055	-0.0741	-0.0194	-0.0563	0.0054	1			
IIV of BA	0.177	0.21	0.248	0.255	0.0173	0.238	0.0481	-0.0236	1		
IIV of Gamma	0.193	-0.139	-0.5	-0.378	-0.101	0.107	0.0095	0.0183	0.14	1	
IIV of error	0.0198	0.0392	0.0159	-0.0085	-0.0099	0.0613	-0.0566	-0.0169	0.0228	-0.13	1

CL/F; Apparent oral clearance, V_c/F; Apparent volume of central compartment, Q/F; Apparent intercompartmental clearance, V_P/F; Apparent volume of peripheral compartment, Ka; Absorption rate constant, F1; Proportionality constant for fraction of first-order absorption process, D2; Virtual duration of dosing for zero order absorption, Lag1; Lag time for first-order absorption, BA; Bioavailability of fed state when that of fasting state was assumed to be 1, Gamma; shape factor for absorption, IIV; inter-individual variability, error; inter-individual variability in residual error

Table 5. Correlation coefficient between inter-occasional variability terms

	IOV of CL/F	IOV of V_c/F	IOV of D2
IOV of CL/F	1		
IOV of V_c/F	0.0367	1	
IOV of D2	0.0163	0.0371	1

CL/F; Apparent oral clearance, V_c/F; Apparent volume of central compartment, D2; Virtual duration of dosing for zero order absorption, IOV; inter-occasion variability

Model evaluation

The population and individual predicted fimasartan concentration by the population PK model versus the observed fimasartan concentration were distributed randomly around the line of identity (Figure 8). Furthermore, the results of the VPC performed based on the final population PK model showed that the most of observed concentrations were within 90^{th} percentile prediction intervals of VPC (Figure 9, 10).

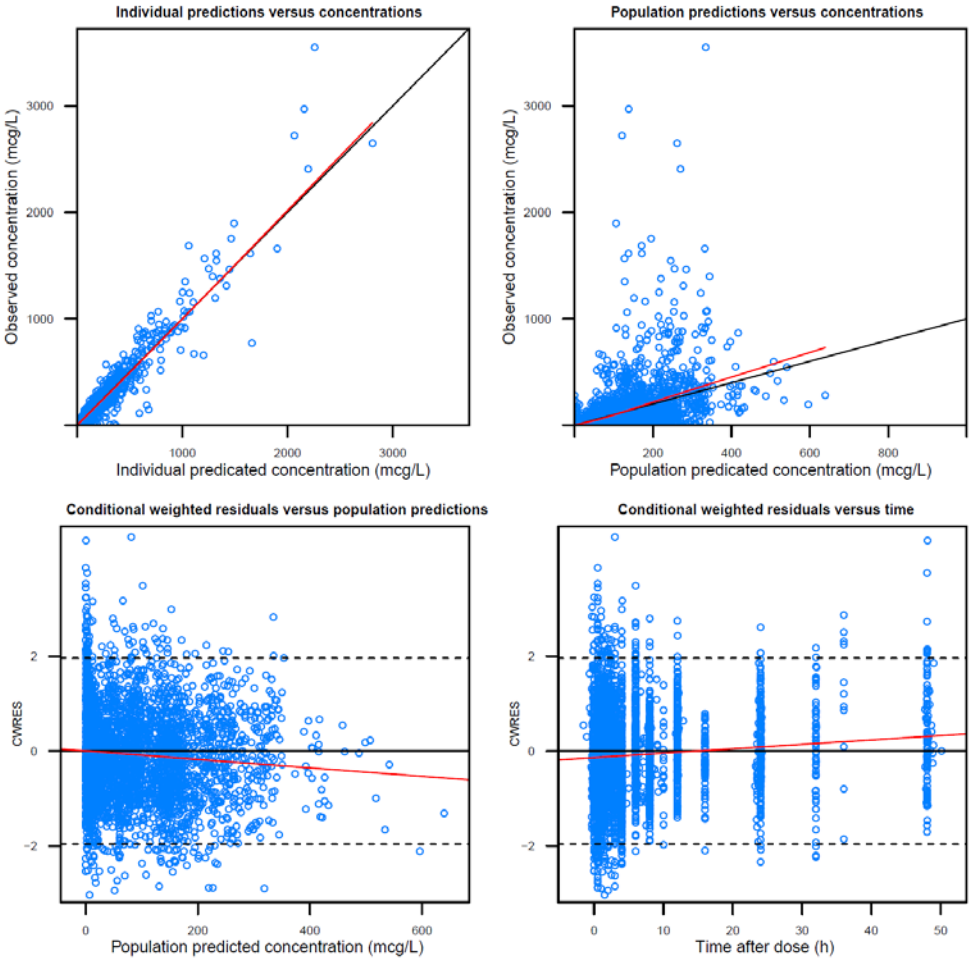


Figure 8 Basic goodness-of-fit plots of the final model for fimasartan; CWRES: conditional weighted residuals; open circles indicate observations; solid black lines are lines of identity. Red lines are LOESS (locally weighted regression)-smoothed lines

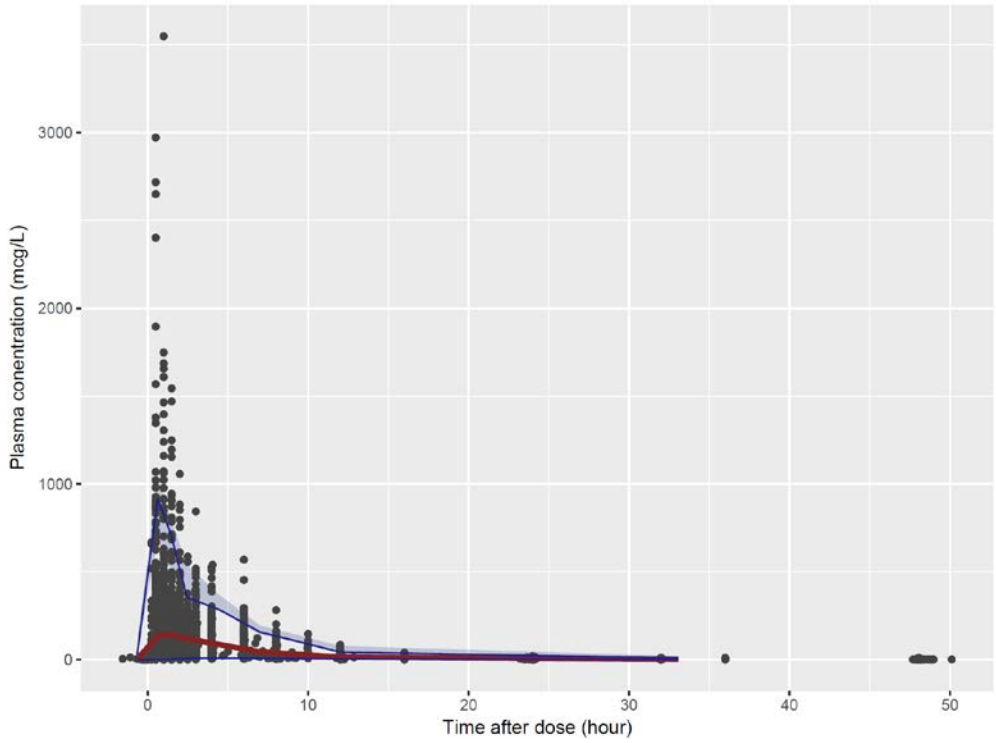
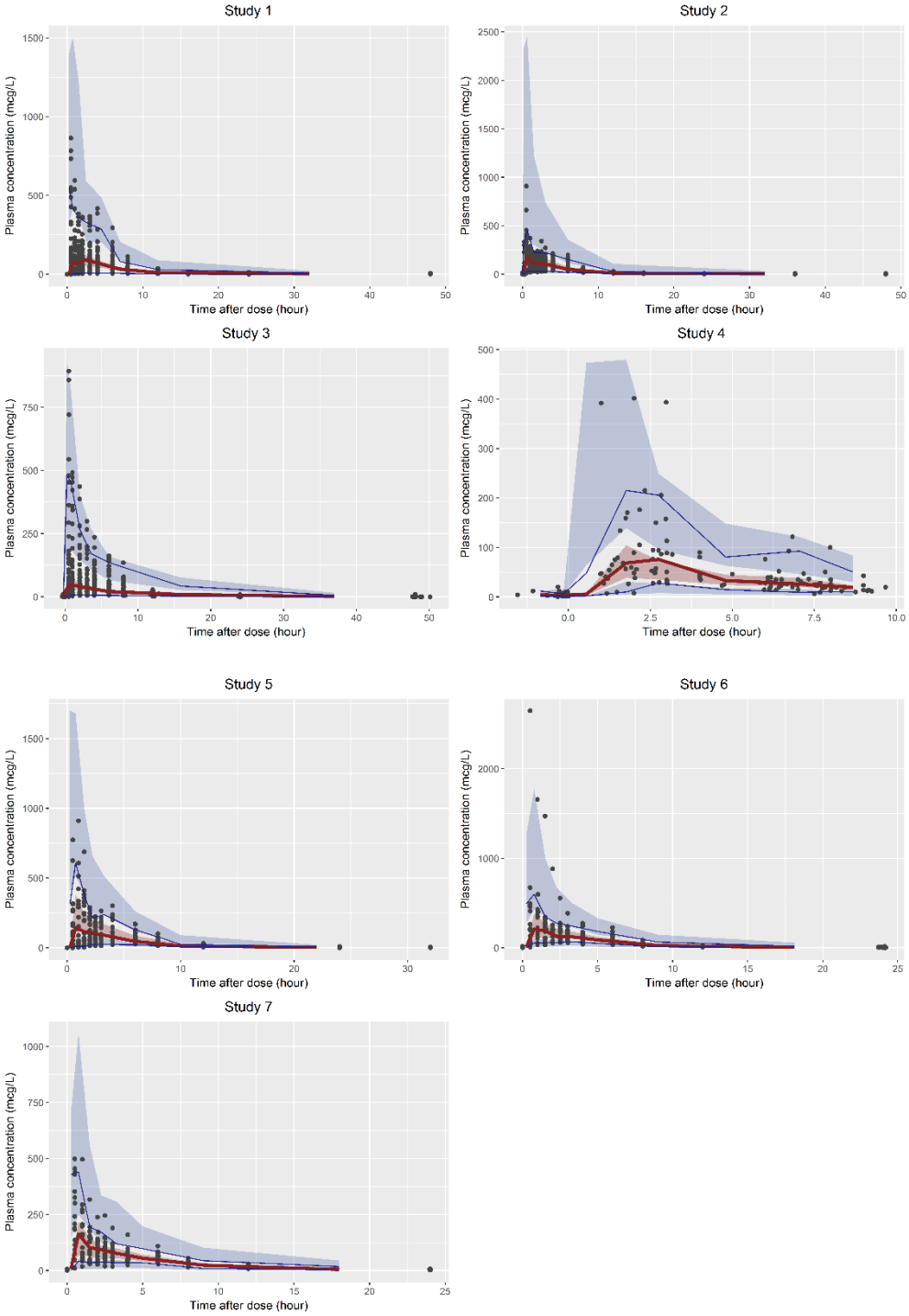
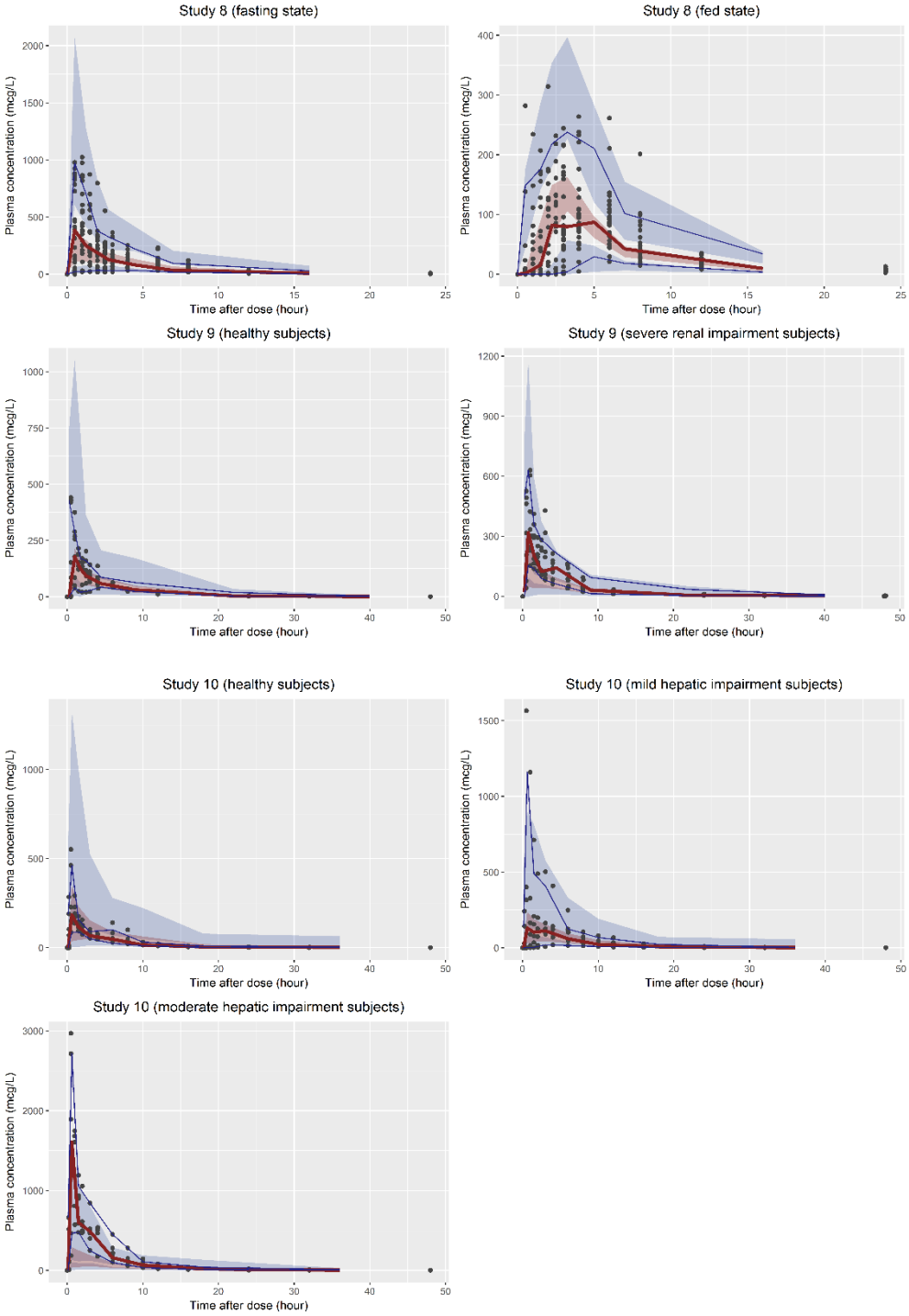


Figure 9 Visual predictive check with 90% interpercentile range for the final model (dark circle: observed concentration, upper blue line: the 95th value of observed concentration, red line: the median of observed concentration, lower blue line: the 5th value of observed concentration, upper blue area: the 95th value of concentration predicted by model, red area: the median value of concentration predicted by model, lower blue area: the 5th value of concentration predicted by model)


Study 1
Plasma concentration (mcg/L)
Time after dose (hour)
Study 2
Plasma concentration (mcg/L)
Time after dose (hour)
Study 3
Plasma concentration (mcg/L)
Time after dose (hour)
Study 4
Plasma concentration (mcg/L)
Time after dose (hour)
Study 5
Plasma concentration (mcg/L)
Time after dose (hour)
Study 6
Plasma concentration (mcg/L)
Time after dose (hour)
Study 7
Plasma concentration (mcg/L)
Time after dose (hour)


Study 8 (fasting state)
Plasma concentration (mcg/L)
Time after dose (hour)
Study 8 (fed state)
Plasma concentration (mcg/L)
Time after dose (hour)
Study 9 (healthy subjects)
Plasma concentration (mcg/L)
Time after dose (hour)
Study 9 (severe renal impairment subjects)
Plasma concentration (mcg/L)
Time after dose (hour)
Study 10 (healthy subjects)
Plasma concentration (mcg/L)
Time after dose (hour)
Study 10 (mild hepatic impairment subjects)
Plasma concentration (mcg/L)
Time after dose (hour)
Study 10 (moderate hepatic impairment subjects)
Plasma concentration (mcg/L)
Time after dose (hour)

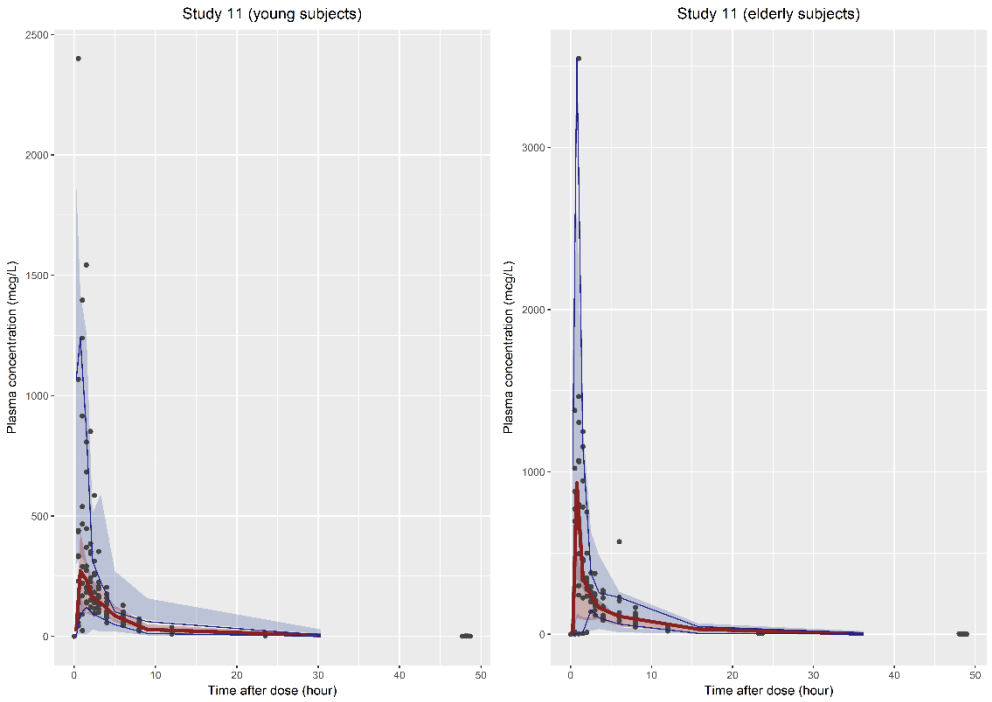


Figure 10 Visual predictive check with 90% interpercentile range for the final model in each study (dark circle: observed concentration, upper blue line: the 95th value of observed concentration, red line: the median of observed concentration, lower blue line: the 5th value of observed concentration, upper blue area: the 95th value of concentration predicted by model, red area: the median value of concentration predicted by model, lower blue area: the 5th value of concentration predicted by model)

Discussion

The population PK model of fimasartan in this study was developed based on the pooled pharmacokinetic data from the 11 clinical trial studies. Typical values, IIV and IOV for PK parameters of fimasartan were obtained by the population PK model considering characteristics in healthy subjects, hypertension patients, and special populations and food effect on fimasartan. Furthermore, significant covariates on PK parameters of fimasartan were selected.

The concentration profile of fimasartan under fasting state in healthy subjects, hypertension patients, and special populations were well described by a two-compartment disposition, first-order elimination model with a mixed absorption model and lag-time (Figure 1, 2, 3, 4, 5, and 6), which was consistent with the previous study. Furthermore, the typical values of PK parameters for population PK model between this study and the previous study were somewhat different but comparable.[15] However, the population PK model in our study combined two absorption models, the mixed absorption model under fasting state and Weibull absorption model under fed state, to adequately describe effect of food on fimasartan absorption. Furthermore, our study divided error model into the two error models because there are two bioanalytical institutes to analyze fimasartan concentration in our study. The error models were all proportional models (Figure 1, 2, 3, 4, 5, and 6 and Table 3).

Fimasartan was approved to be administered regardless of food intake by the Ministry of Food and Drug Safety in South Korea (Label for fimasartan, Boryung Pharmaceutical Corp., Inc., Seoul, South Korea). However, time concentration profiles of fimasartan between under fasting and fed state in the study 8 were considerably different (Figure 5a, and b). Food have been known to lower gastric emptying rate, which may induce a delayed absorption of fimasartan.[16] Furthermore, food elevated PH at the intestine, which induce a result of the increased ionized form of fimasartan because fimasartan is an acidic drug with a PKa value of 5.19.[17] As a result, concentration profile of fimasartan under fed state with a high fat diet showed the considerably delayed absorption, decreased C_{max} and sigmoidal absorption pattern.[18] Furthermore, the mixed absorption model in our model did not adequately describe absorption profile of fimasartan after food intake. Therefore, an absorption model of fimasartan under fed state in study 8 was needed, and hence various absorption models were evaluated. As a result, the Weibull model was selected and incorporated as the absorption model of fimasartan under fed state, which was consistent with the previous study.[18] The population PK model in this study showed that the relative bioavailability decreased by 38 % under fed state (Table 3).

Analysis of covariates indicated that several demographic and clinical factors affect PK parameters of fimasartan. Among them, the most effective covariate on PK parameters of fimasartan was body weight and then, body weight was contained within CL/F, V_c/F, Q/F, V_p/F. This finding was consistent with the results of previous study, while all exponent values of body weight on CL/F, V_c/F, Q/F, V_p/F

in this study were smaller than those in previous study (Table 3).[15] Therefore, it was predicted that exposure changes of fimasartan by body weight were smaller than those predicted in the previous study.[15] However, further simulation using our study results is necessary to confirm exposure change of fimasartan by body weight.

Because fimasartan was mainly excreted via bile to feces and metabolized by CYP3A4, hepatic dysfunction could affect the CL/F of fimasartan.[8,19,20] Hepatic impairment status in the final population PK model was identified as a significant covariate influencing CL/F of fimasartan, which supported hepatic dysfunction's effect. The CL/F of hepatic impairment subjects was 0.36-fold lower than the typical value of CL/F. This finding suggested that exposure of fimasartan in hepatic impairment subjects was increased due to CL/F of fimasartan affected by hepatic function, which was also consistent with the results of clinical study in subjects with hepatic impairment.[20] However, VPC result of study 10 for moderate hepatic impairment subjects showed that our model under-predicted concentrations of fimasartan in moderate hepatic impairment subjects (Figure 10). It is thought that this finding is caused by the difference of concentration-time profiles for fimasartan between mild and moderate hepatic impairment subjects in the study 10 consisted of mild (N = 6) and moderate (N = 6) hepatic impairment subjects and the two subjects groups in the study 10. The additional assessment of hepatic impairment status covariate on CL/F of fimasartan considering difference between two hepatic impairment groups may improve the model predictability.

The previous studies reported that renal impairment and age more than 65 years affected PK parameters of fimasartan.[21,22] However, our dataset included the small number of renal impairment (N=8) and elderly subjects (N=14). Furthermore, our dataset included only severe renal impairment subjects without mild and moderate renal impairment subjects. Therefore, to adequately assess effects of renal impairments status and age more than 65 years on PK parameters of fimasartan, further studies to incorporate more data for mild and moderate renal impairment subjects and elderly subjects into our population PK model may be helpful.

Conclusion

The observed plasma concentrations of fimasartan in a variety population groups were well described by the population PK model. Body weight and hepatic impairment status was selected as significant covariate of the final population PK model for fimasartan

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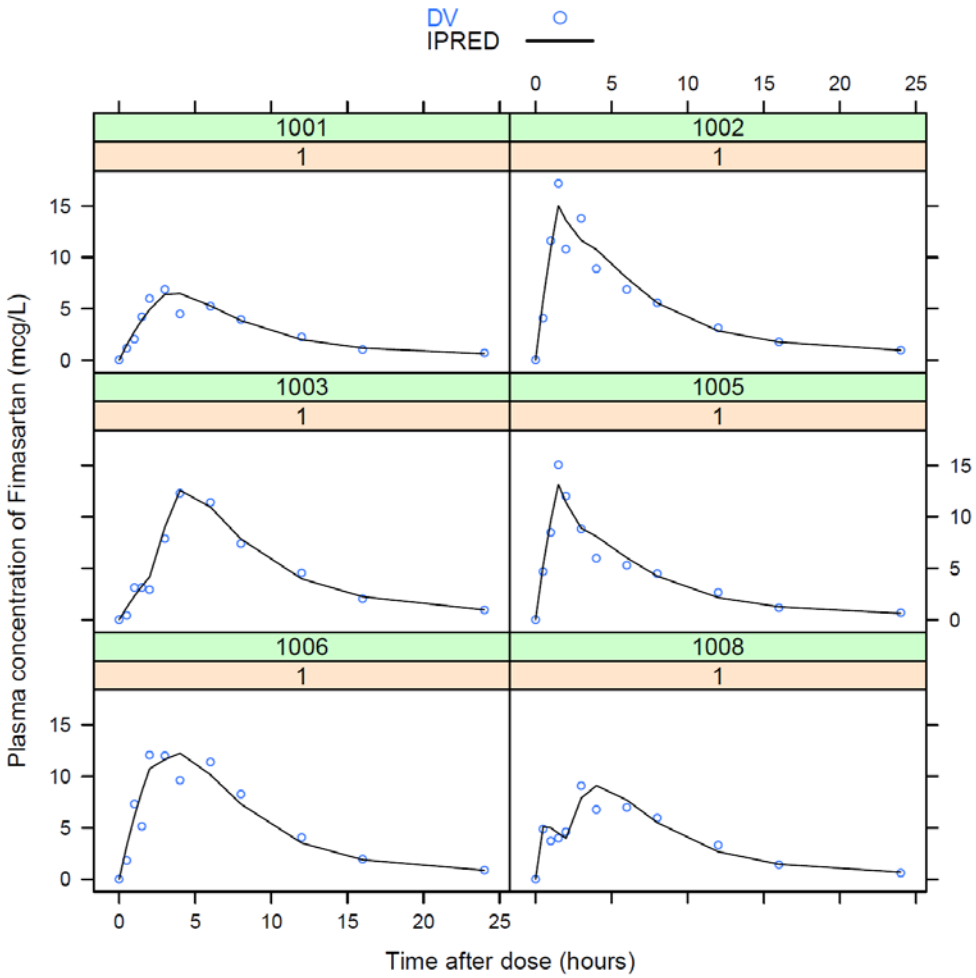
APPENDICES

1. Individual fitting plot for the final pharmacokinetic model in study 1

Study 1 group: 1001-1008 (20 mg), 1009-1016 (60 mg), 1017-1024 (120 mg), 1025-1032 (240 mg), 1033-1040 (480 mg)

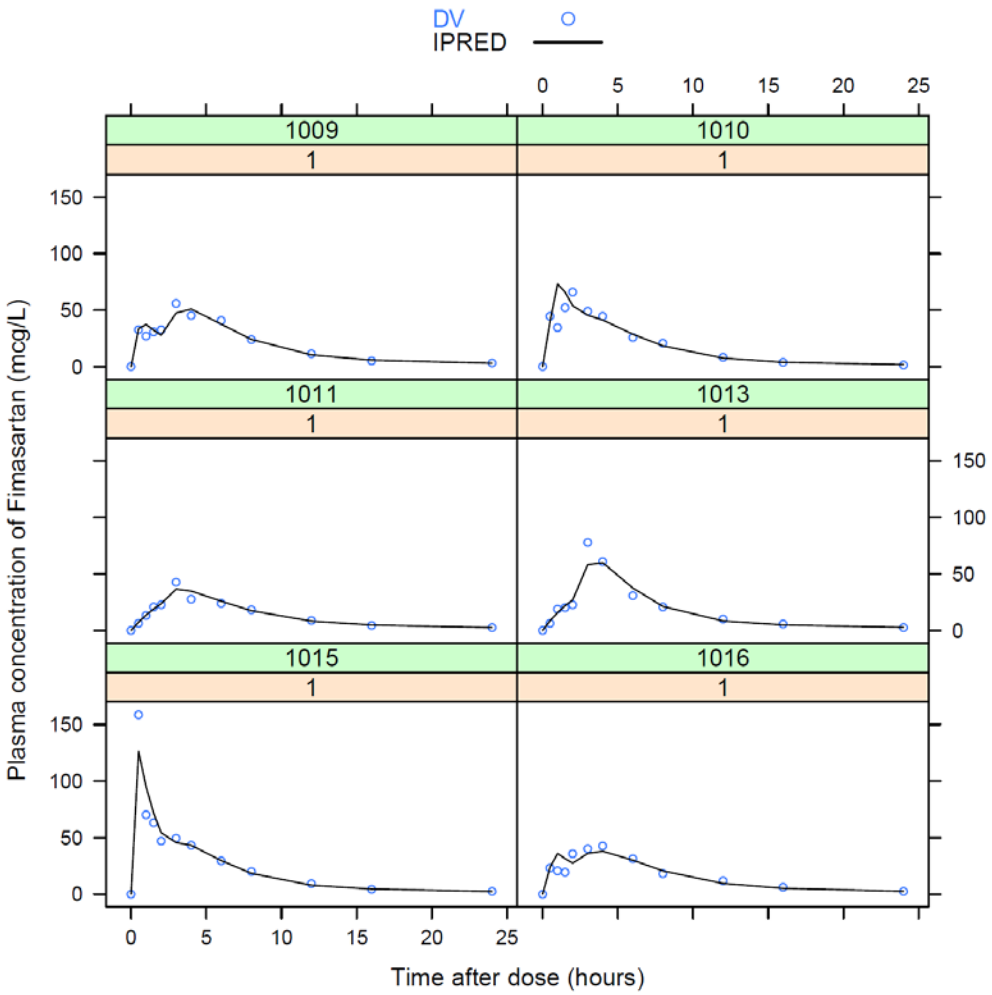
1, 2: occasion period (1=period 1, 2=period 2)



Individual fitting plot for the final pharmacokinetic model in study 1 (continuous)

Study 1 group: 1001-1008 (20 mg), 1009-1016 (60 mg), 1017-1024 (120 mg), 1025-1032 (240 mg), 1033-1040 (480 mg)

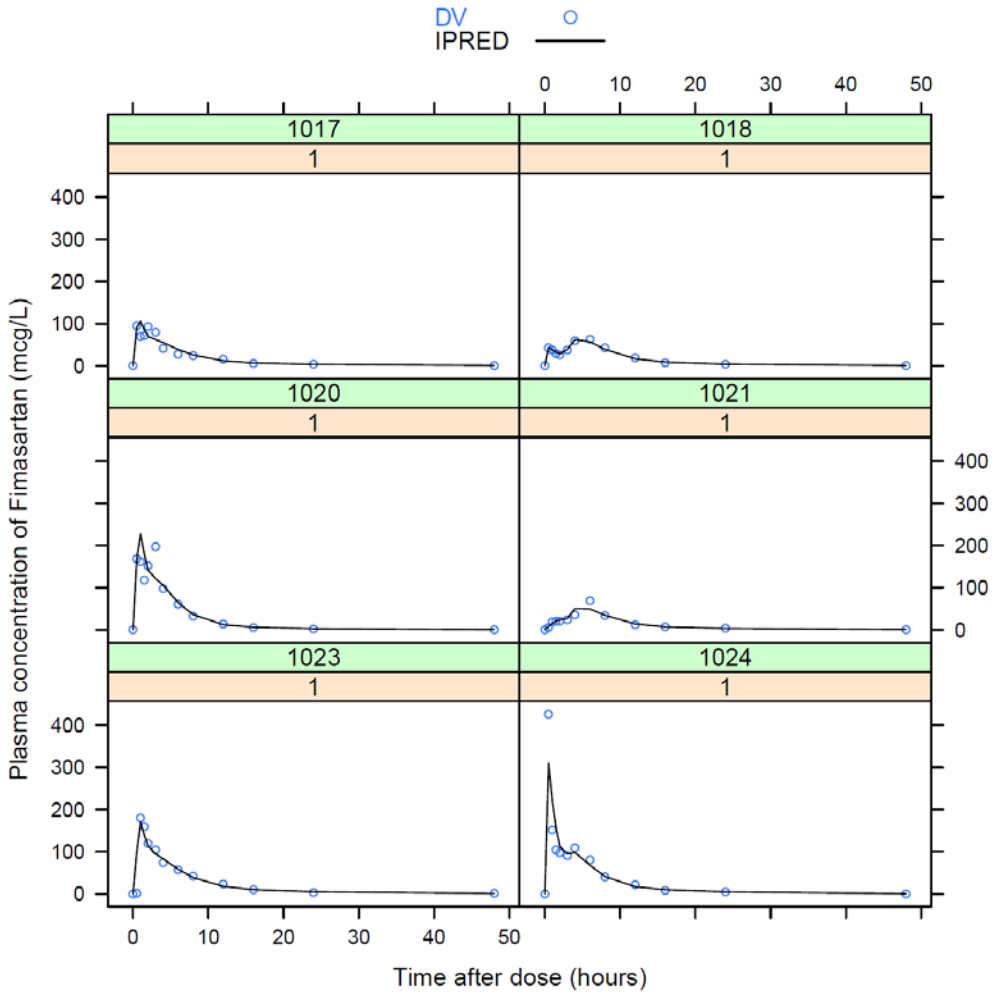
1, 2: occasion period (1=period 1, 2=period 2)



Individual fitting plot for the final pharmacokinetic model in study 1 (continuous)

Study 1 group: 1001-1008 (20 mg), 1009-1016 (60 mg), 1017-1024 (120 mg), 1025-1032 (240 mg), 1033-1040 (480 mg)

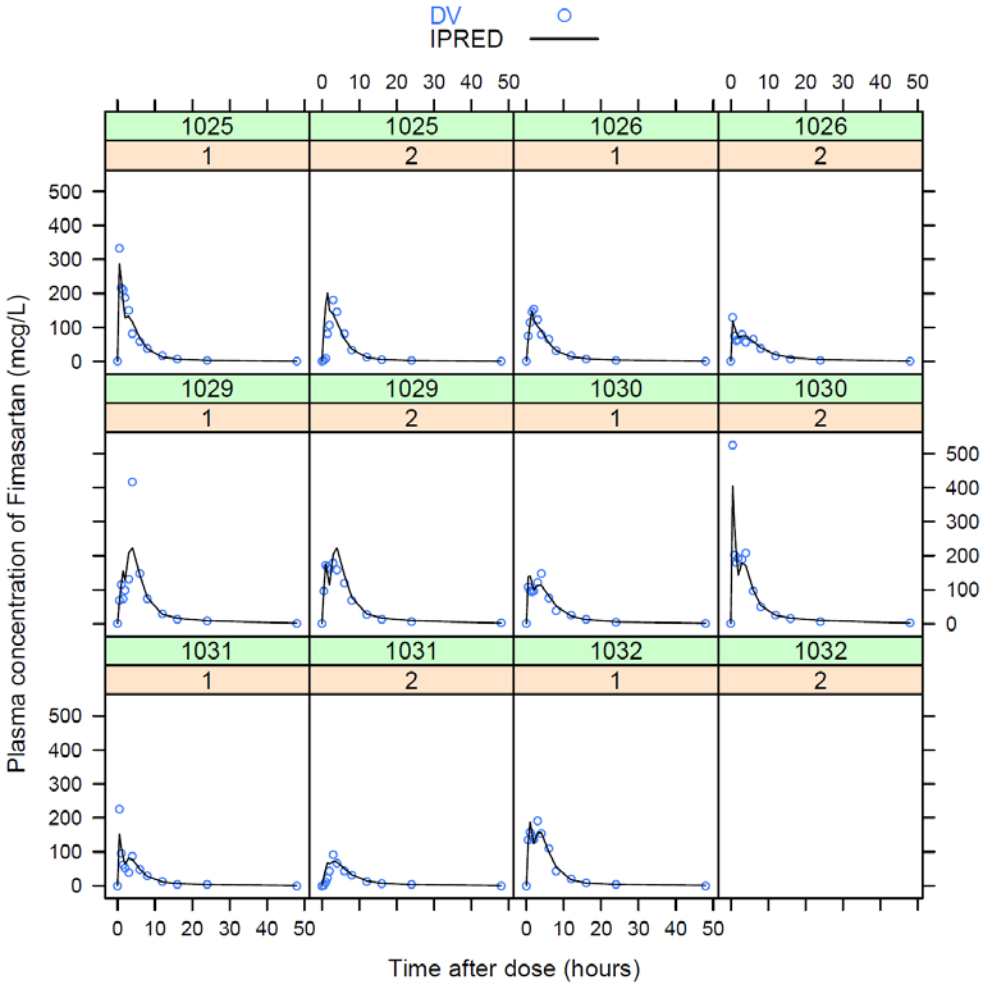
1, 2: occasion period (1=period 1, 2=period 2)



Individual fitting plot for the final pharmacokinetic model in study 1 (continuous)

Study 1 group: 1001-1008 (20 mg), 1009-1016 (60 mg), 1017-1024 (120 mg), 1025-1032 (240 mg), 1033-1040 (480 mg)

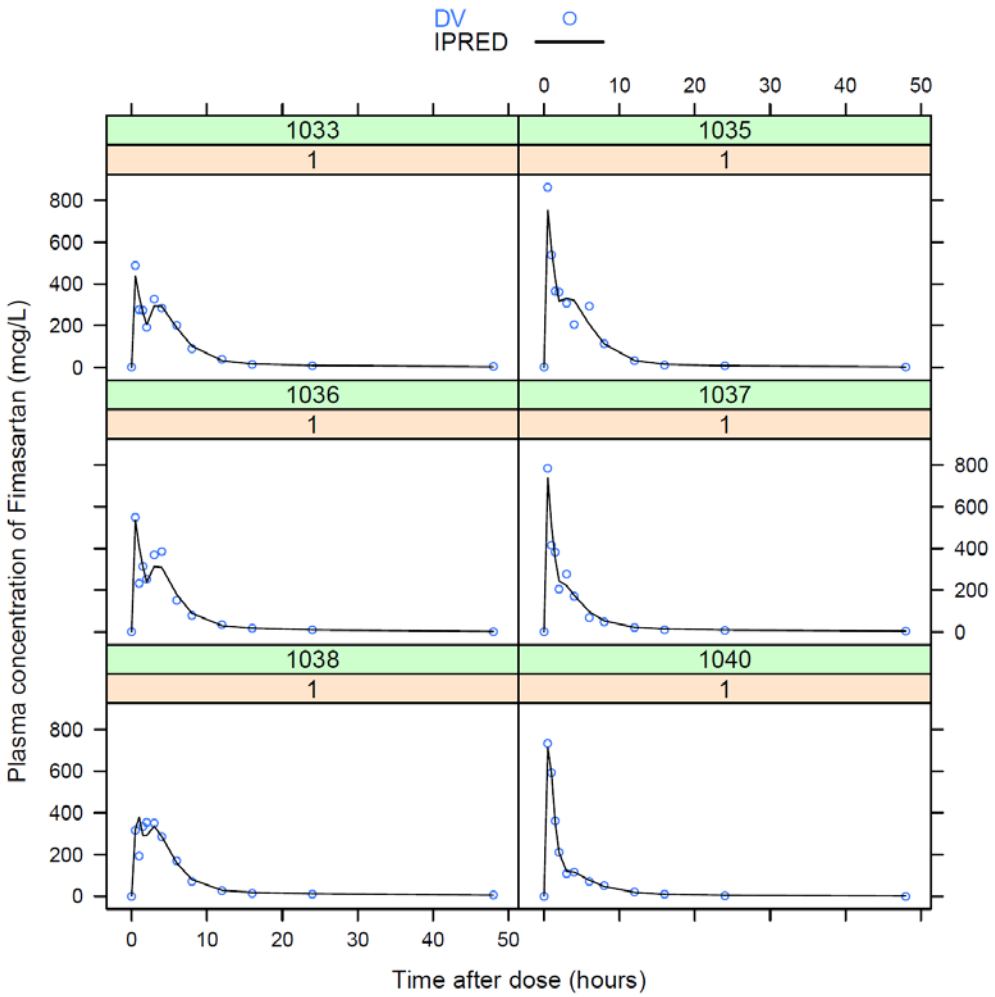
1, 2: occasion period (1=period 1, 2=period 2)



Individual fitting plot for the final pharmacokinetic model in study 1 (continuous)

Study 1 group: 1001-1008 (20 mg), 1009-1016 (60 mg), 1017-1024 (120 mg), 1025-1032 (240 mg), 1033-1040 (480 mg)

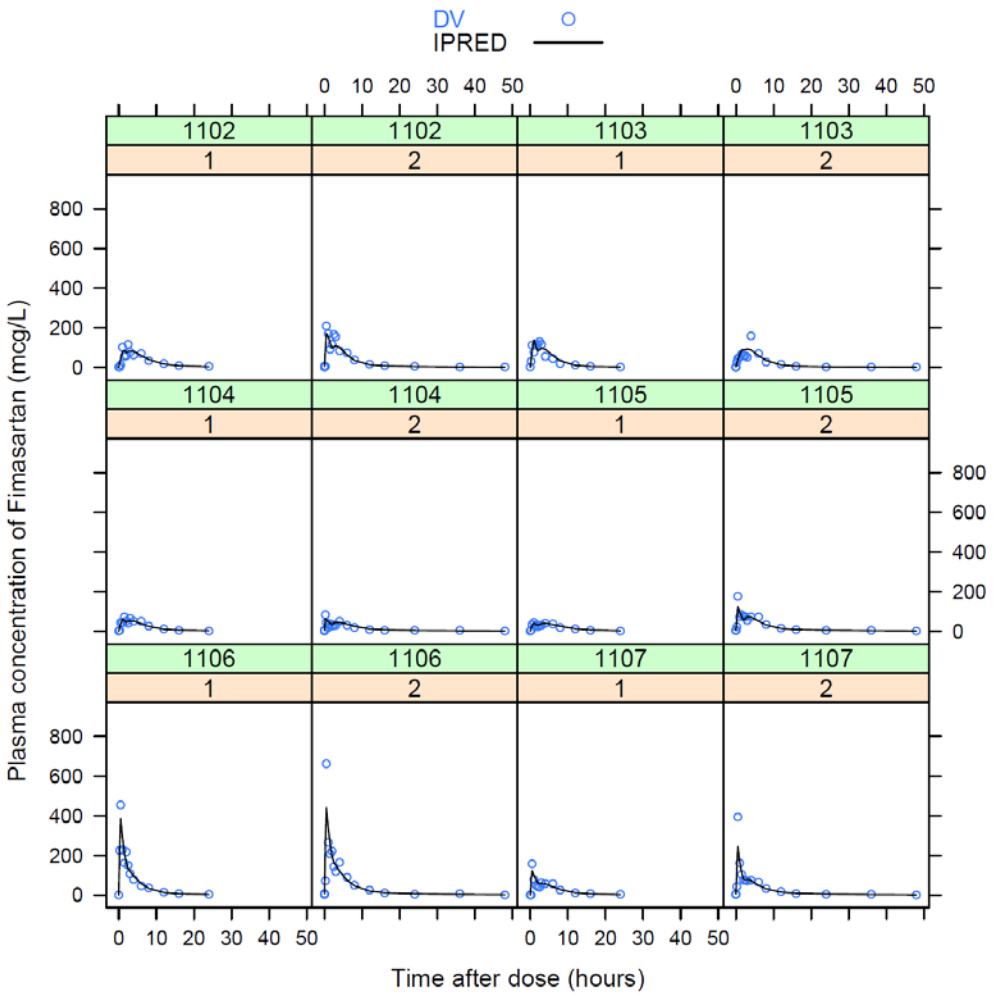
1, 2: occasion period (1=period 1, 2=period 2)



2. Individual fitting plot for the final pharmacokinetic model in study 2

Study 2 group: 1102-1107 (120 mg), 1109-1116 (360 mg)

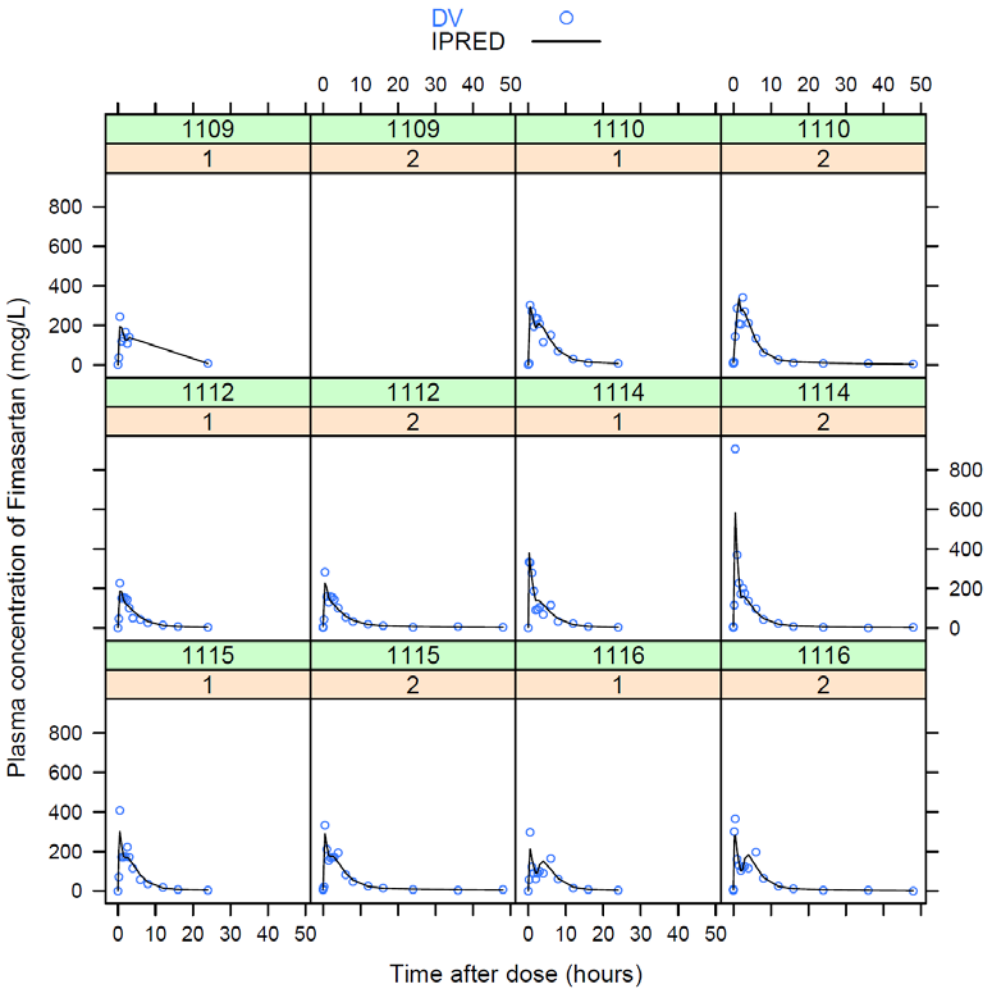
1, 2: occasion period (1=period 1, 2=period 2)



Individual fitting plot for the final pharmacokinetic model in study 2 (continuous)

Study 2 group: 1102-1107 (120 mg), 1109-1116 (360 mg)

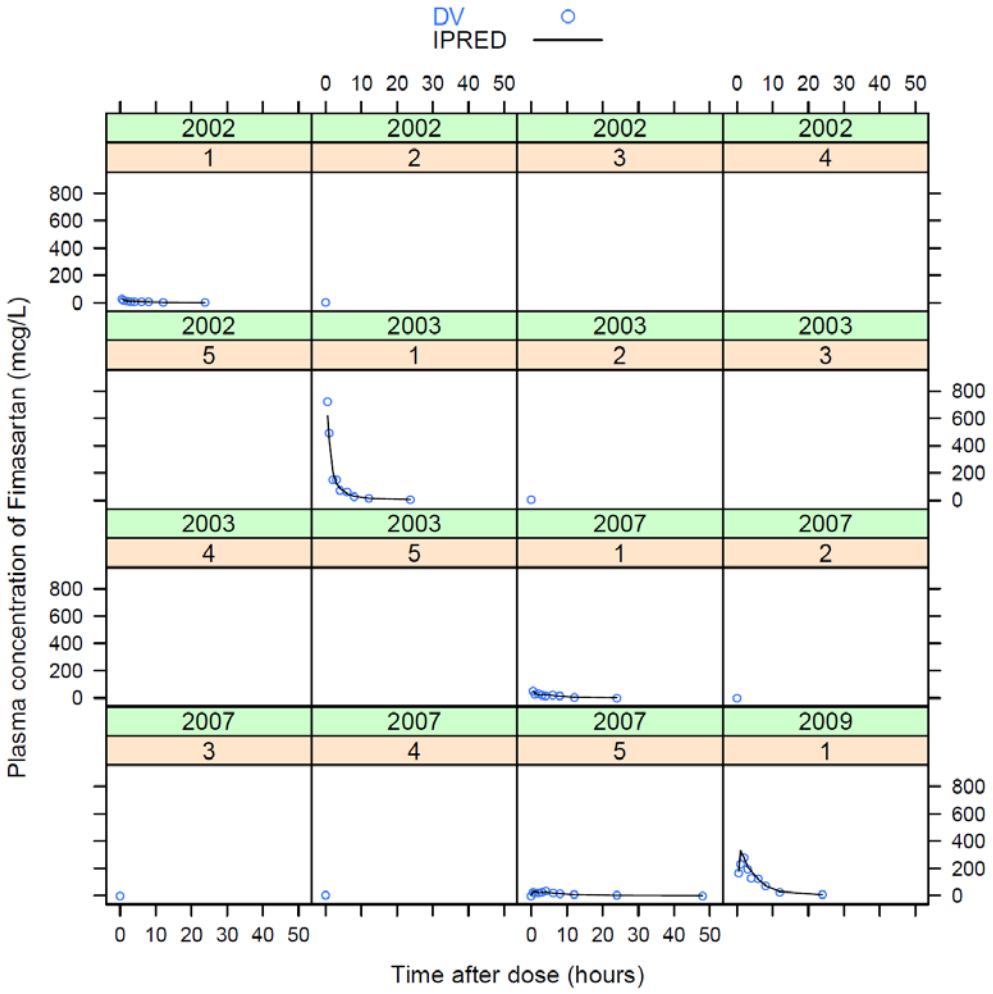
1, 2: occasion period (1=period 1, 2=period 2)



3. Individual fitting plot for the final pharmacokinetic model in study 3

Study 3 group: 2002, 2012, 2016, 2020, 2030, 2032, 2039, 2040, 2044 (20 mg), 2007, 2011, 2018, 2023, 2025, 2038, 2043, 2046, 2049 (60 mg), 2003, 2009, 2014, 2022, 2027, 2031, 2034, 2042 (180 mg)

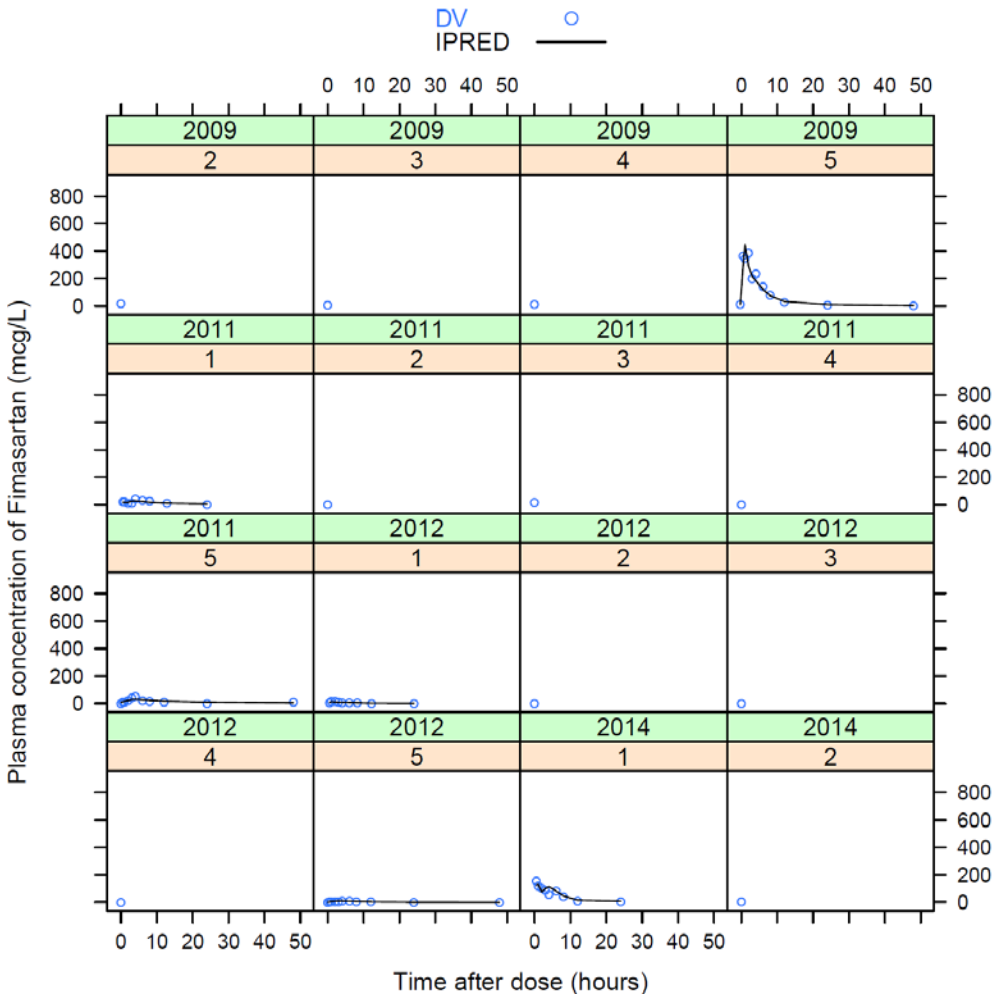
1, 2, 3, 4, 5: occasion period (1=period 1, 2=period 2, 3=period 3, 4=period 4, 5=period 5)



Individual fitting plot for the final pharmacokinetic model in study 3 (continuous)

Study 3 group: 2002, 2012, 2016, 2020, 2030, 2032, 2039, 2040, 2044 (20 mg), 2007, 2011, 2018, 2023, 2025, 2038, 2043, 2046, 2049 (60 mg), 2003, 2009, 2014, 2022, 2027, 2031, 2034, 2042 (180 mg)

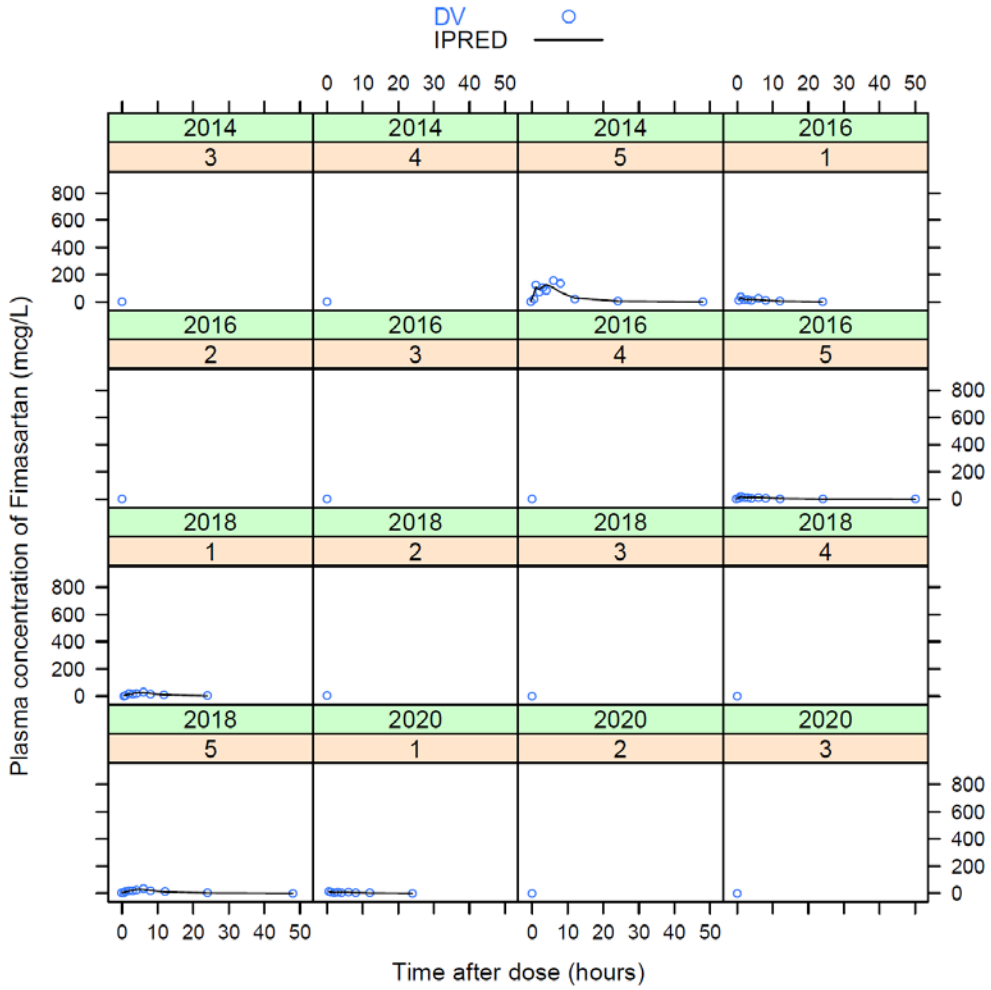
1, 2, 3, 4, 5: occasion period (1=period 1, 2=period 2, 3=period 3, 4=period 4, 5=period 5)



Individual fitting plot for the final pharmacokinetic model in study 3 (continuous)

Study 3 group: 2002, 2012, 2016, 2020, 2030, 2032, 2039, 2040, 2044 (20 mg), 2007, 2011, 2018, 2023, 2025, 2038, 2043, 2046, 2049 (60 mg), 2003, 2009, 2014, 2022, 2027, 2031, 2034, 2042 (180 mg)

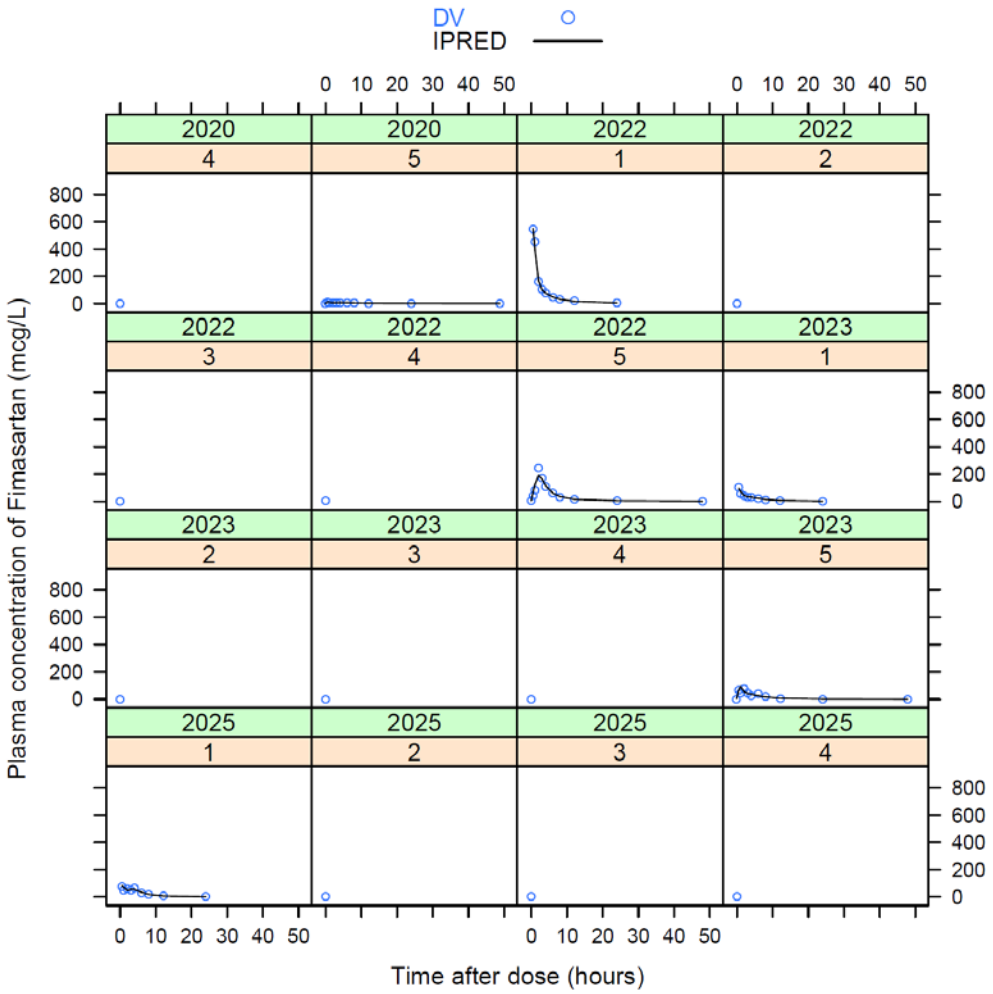
1, 2, 3, 4, 5: occasion period (1=period 1, 2=period 2, 3=period 3, 4=period 4, 5=period 5)



Individual fitting plot for the final pharmacokinetic model in study 3 (continuous)

Study 3 group: 2002, 2012, 2016, 2020, 2030, 2032, 2039, 2040, 2044 (20 mg), 2007, 2011, 2018, 2023, 2025, 2038, 2043, 2046, 2049 (60 mg), 2003, 2009, 2014, 2022, 2027, 2031, 2034, 2042 (180 mg)

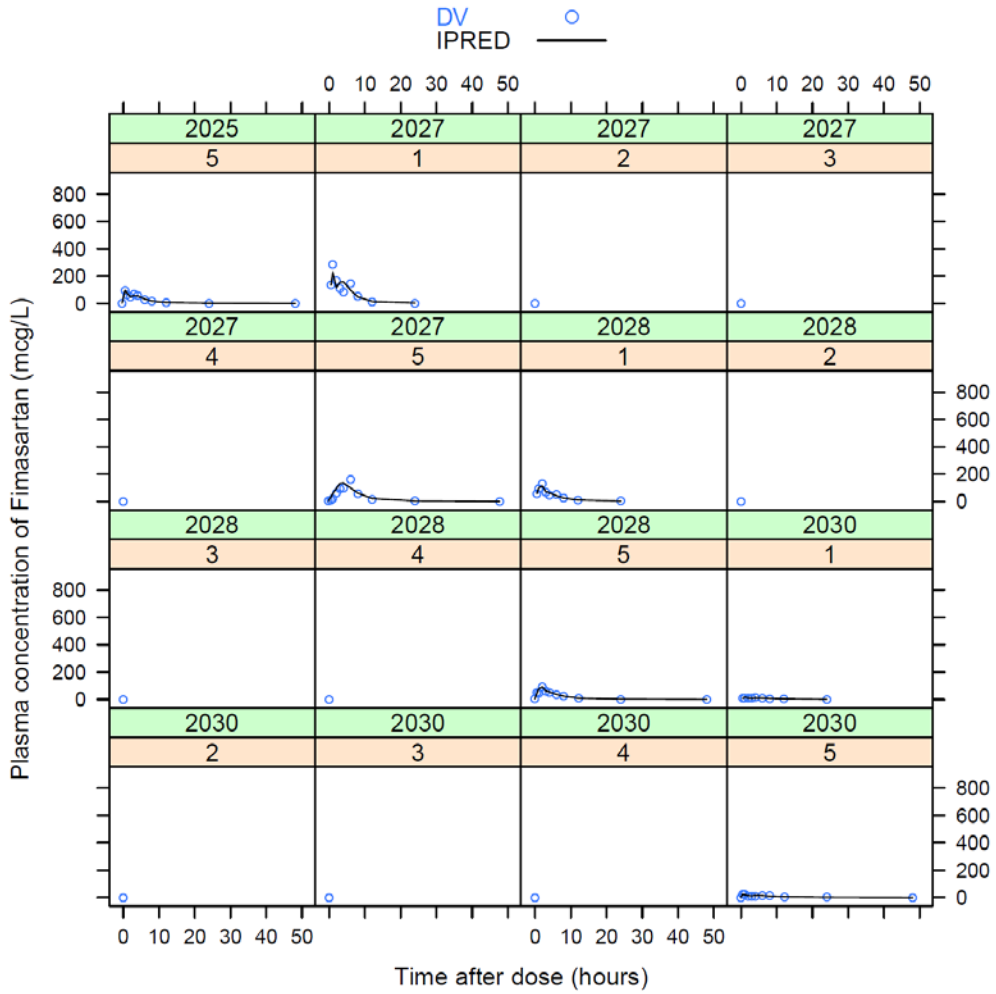
1, 2, 3, 4, 5: occasion period (1=period 1, 2=period 2, 3=period 3, 4=period 4, 5=period 5)



Individual fitting plot for the final pharmacokinetic model in study 3 (continuous)

Study 3 group: 2002, 2012, 2016, 2020, 2030, 2032, 2039, 2040, 2044 (20 mg), 2007, 2011, 2018, 2023, 2025, 2038, 2043, 2046, 2049 (60 mg), 2003, 2009, 2014, 2022, 2027, 2031, 2034, 2042 (180 mg)

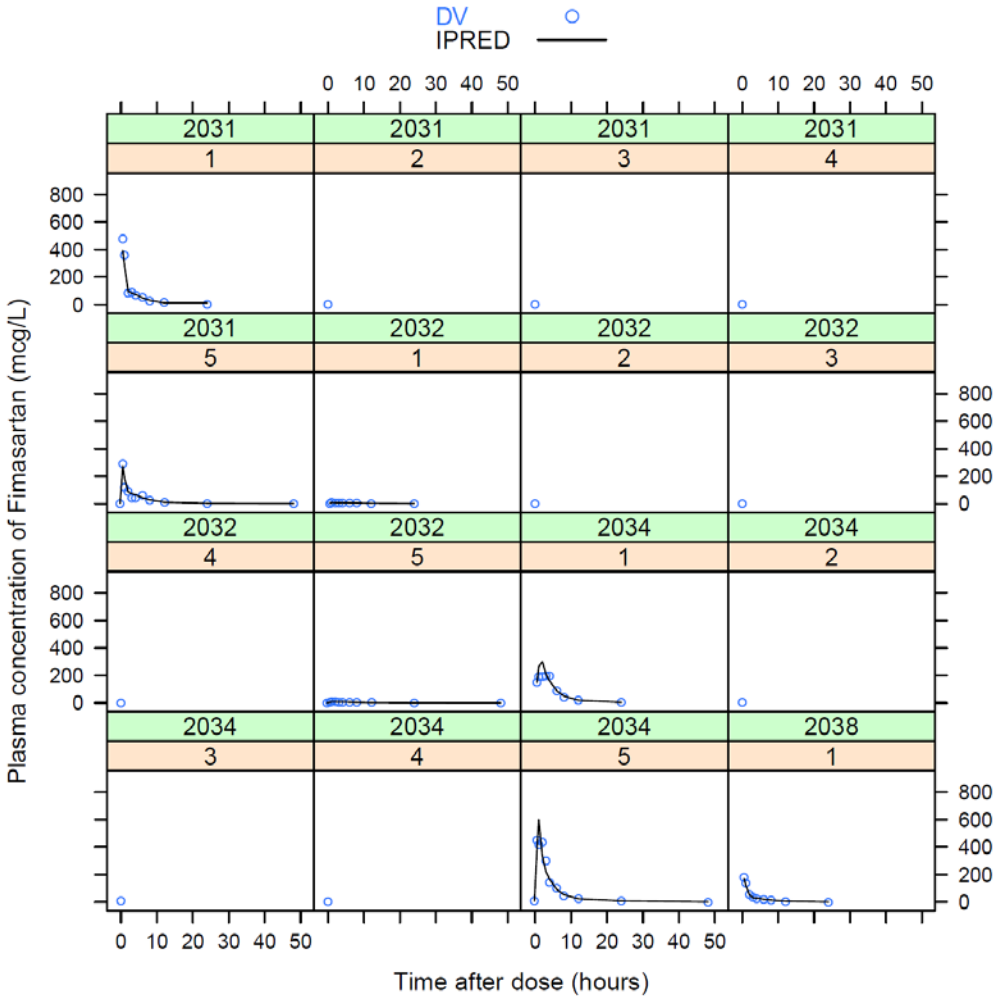
1, 2, 3, 4, 5: occasion period (1=period 1, 2=period 2, 3=period 3, 4=period 4, 5=period 5)



Individual fitting plot for the final pharmacokinetic model in study 3 (continuous)

Study 3 group: 2002, 2012, 2016, 2020, 2030, 2032, 2039, 2040, 2044 (20 mg), 2007, 2011, 2018, 2023, 2025, 2038, 2043, 2046, 2049 (60 mg), 2003, 2009, 2014, 2022, 2027, 2031, 2034, 2042 (180 mg)

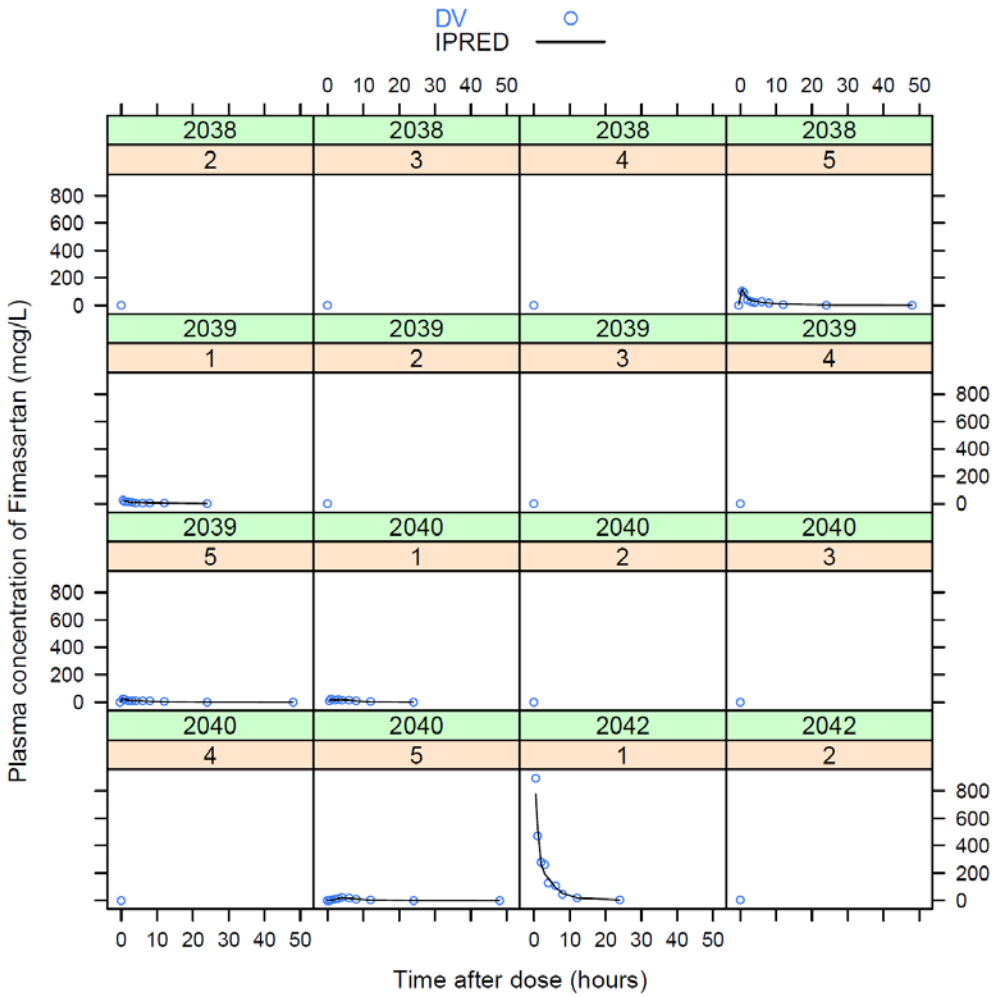
1, 2, 3, 4, 5: occasion period (1=period 1, 2=period 2, 3=period 3, 4=period 4, 5=period 5)



Individual fitting plot for the final pharmacokinetic model in study 3 (continuous)

Study 3 group: 2002, 2012, 2016, 2020, 2030, 2032, 2039, 2040, 2044 (20 mg), 2007, 2011, 2018, 2023, 2025, 2038, 2043, 2046, 2049 (60 mg), 2003, 2009, 2014, 2022, 2027, 2031, 2034, 2042 (180 mg)

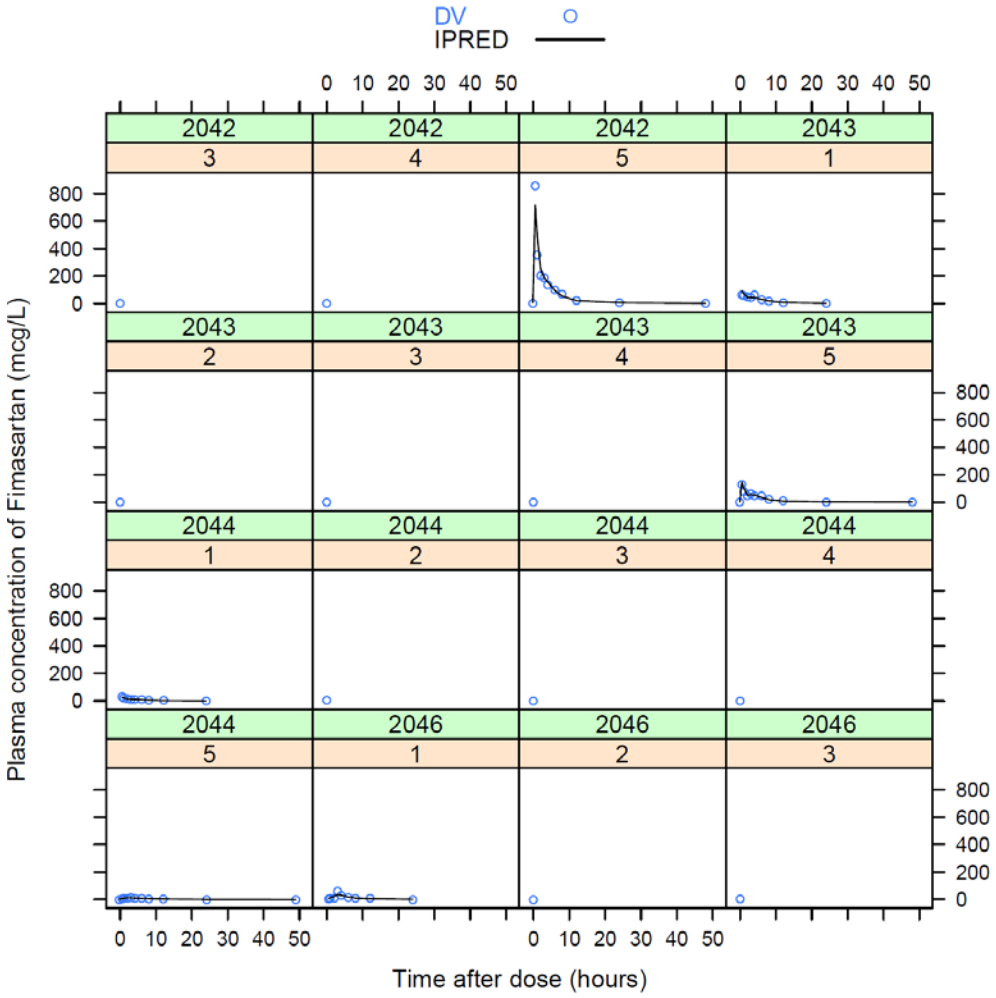
1, 2, 3, 4, 5: occasion period (1=period 1, 2=period 2, 3=period 3, 4=period 4, 5=period 5)



Individual fitting plot for the final pharmacokinetic model in study 3 (continuous)

Study 3 group: 2002, 2012, 2016, 2020, 2030, 2032, 2039, 2040, 2044 (20 mg), 2007, 2011, 2018, 2023, 2025, 2038, 2043, 2046, 2049 (60 mg), 2003, 2009, 2014, 2022, 2027, 2031, 2034, 2042 (180 mg)

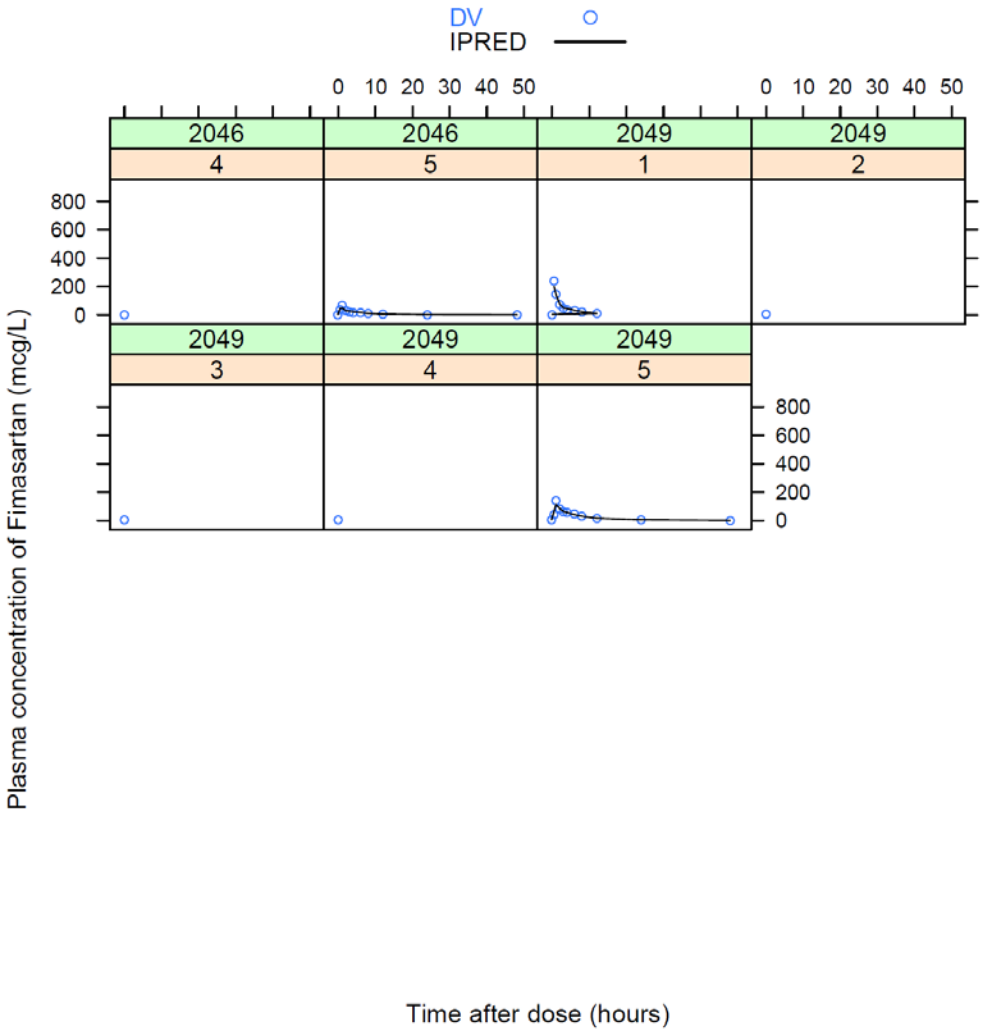
1, 2, 3, 4, 5: occasion period (1=period 1, 2=period 2, 3=period 3, 4=period 4, 5=period 5)



Individual fitting plot for the final pharmacokinetic model in study 3 (continuous)

Study 3 group: 2002, 2012, 2016, 2020, 2030, 2032, 2039, 2040, 2044 (20 mg), 2007, 2011, 2018, 2023, 2025, 2038, 2043, 2046, 2049 (60 mg), 2003, 2009, 2014, 2022, 2027, 2031, 2034, 2042 (180 mg)

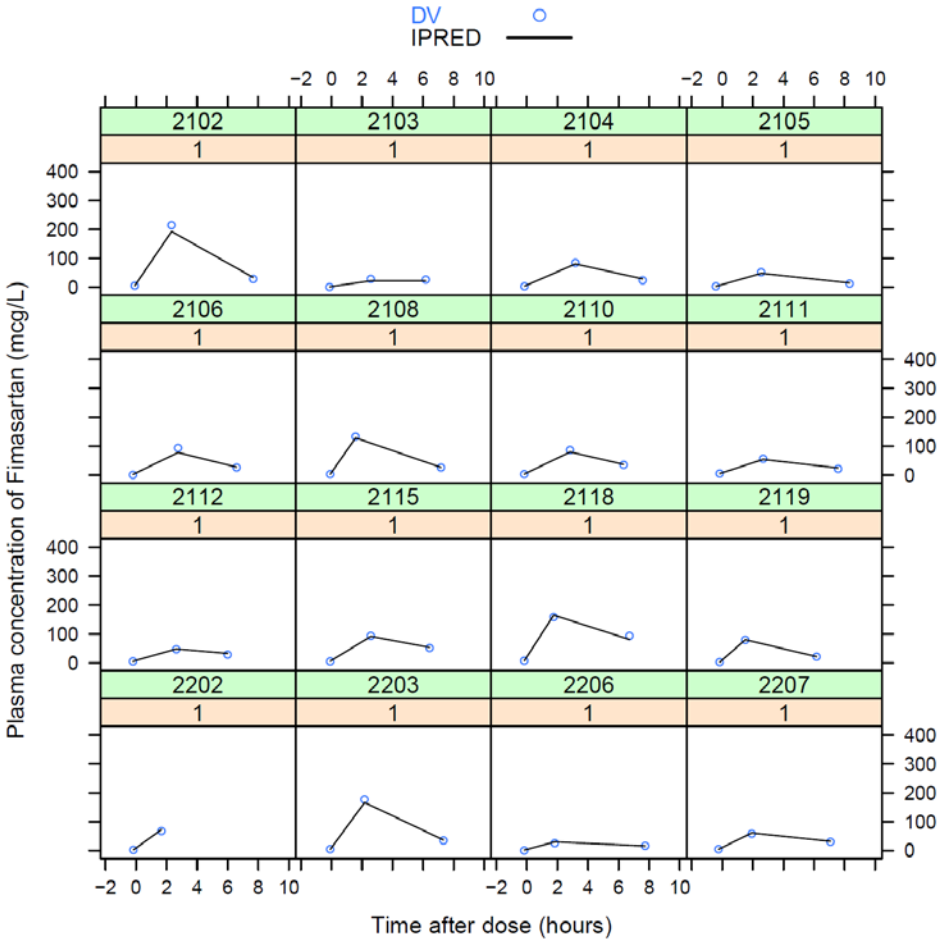
1, 2, 3, 4, 5: occasion period (1=period 1, 2=period 2, 3=period 3, 4=period 4, 5=period 5)



4. Individual fitting plot for the final pharmacokinetic model in study 4

Study 4 group: 2103, 2105, 2108, 2111, 2112, 2119, 2202, 2206, 2209, 2301, 2303, 2309, 2311, 2313, 2314, 2401, 2402, 2410, 2412, 2413, 2418, 2420, 2423, 2501, 2504, 2508, 2510, 2514, 2516, 2521 (60 mg), 2102, 2104, 2106, 2110, 2115, 2118, 2203, 2207, 2208, 2302, 2305, 2307, 2312, 2316, 2403, 2405, 2408, 2409, 2415, 2417, 2421, 2424, 2502, 2503, 2507, 2512, 2518, 2519, 2522 (120 mg)

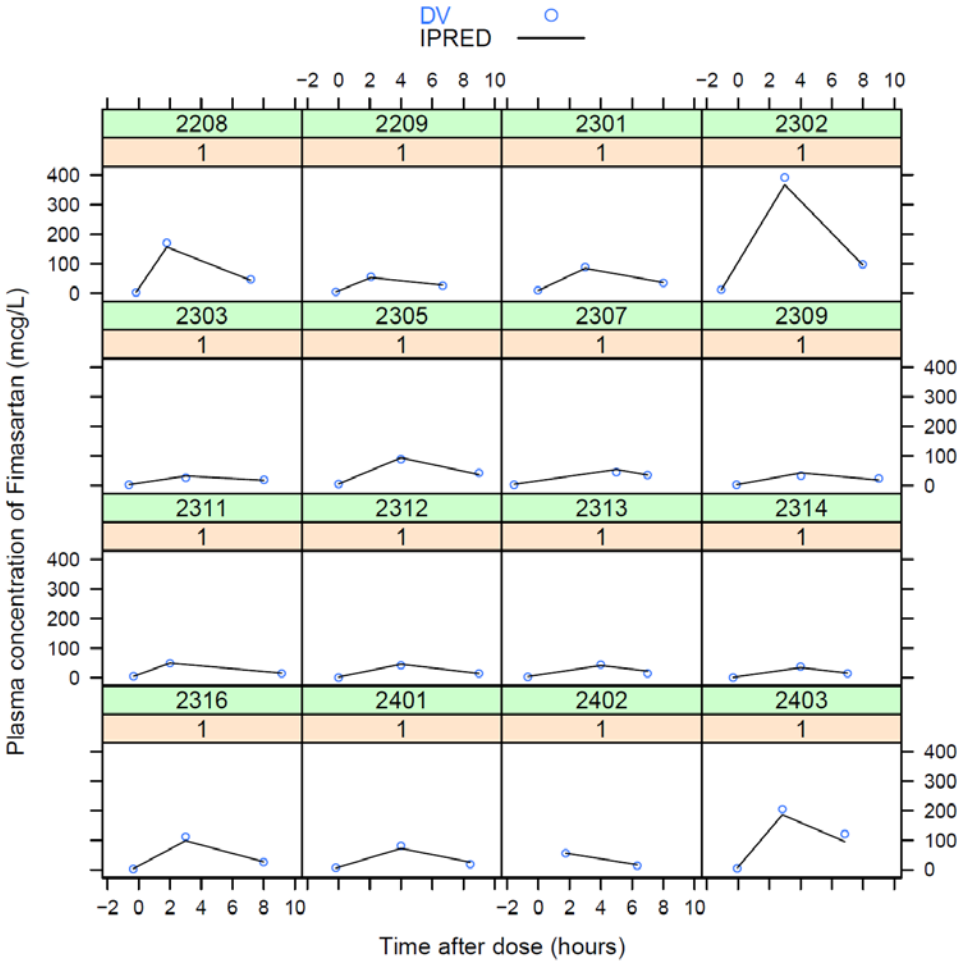
1: occasion period (1=period 1)



Individual fitting plot for the final pharmacokinetic model in study 4 (continuous)

Study 4 group: 2103, 2105, 2108, 2111, 2112, 2119, 2202, 2206, 2209, 2301, 2303, 2309, 2311, 2313, 2314, 2401, 2402, 2410, 2412, 2413, 2418, 2420, 2423, 2501, 2504, 2508, 2510, 2514, 2516, 2521 (60 mg), 2102, 2104, 2106, 2110, 2115, 2118, 2203, 2207, 2208, 2302, 2305, 2307, 2312, 2316, 2403, 2405, 2408, 2409, 2415, 2417, 2421, 2424, 2502, 2503, 2507, 2512, 2518, 2519, 2522 (120 mg)

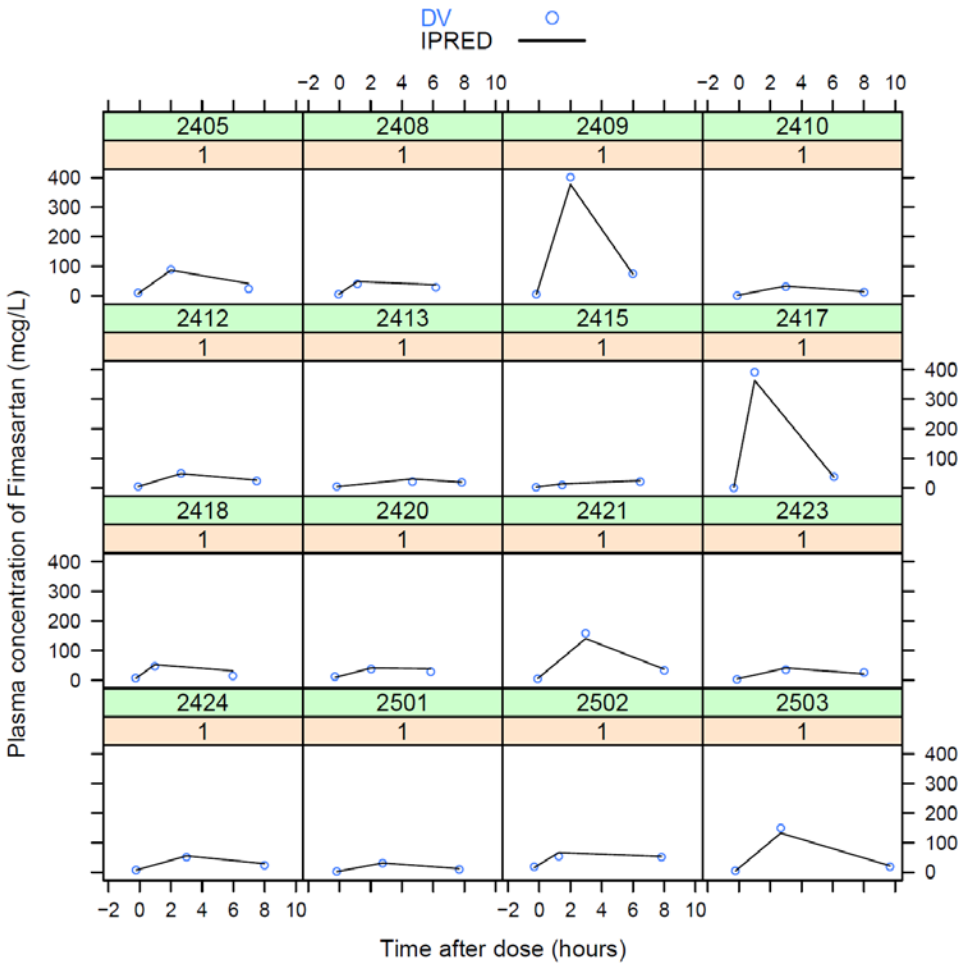
1: occasion period (1=period 1)



Individual fitting plot for the final pharmacokinetic model in study 4 (continuous)

Study 4 group: 2103, 2105, 2108, 2111, 2112, 2119, 2202, 2206, 2209, 2301, 2303, 2309, 2311, 2313, 2314, 2401, 2402, 2410, 2412, 2413, 2418, 2420, 2423, 2501, 2504, 2508, 2510, 2514, 2516, 2521 (60 mg), 2102, 2104, 2106, 2110, 2115, 2118, 2203, 2207, 2208, 2302, 2305, 2307, 2312, 2316, 2403, 2405, 2408, 2409, 2415, 2417, 2421, 2424, 2502, 2503, 2507, 2512, 2518, 2519, 2522 (120 mg)

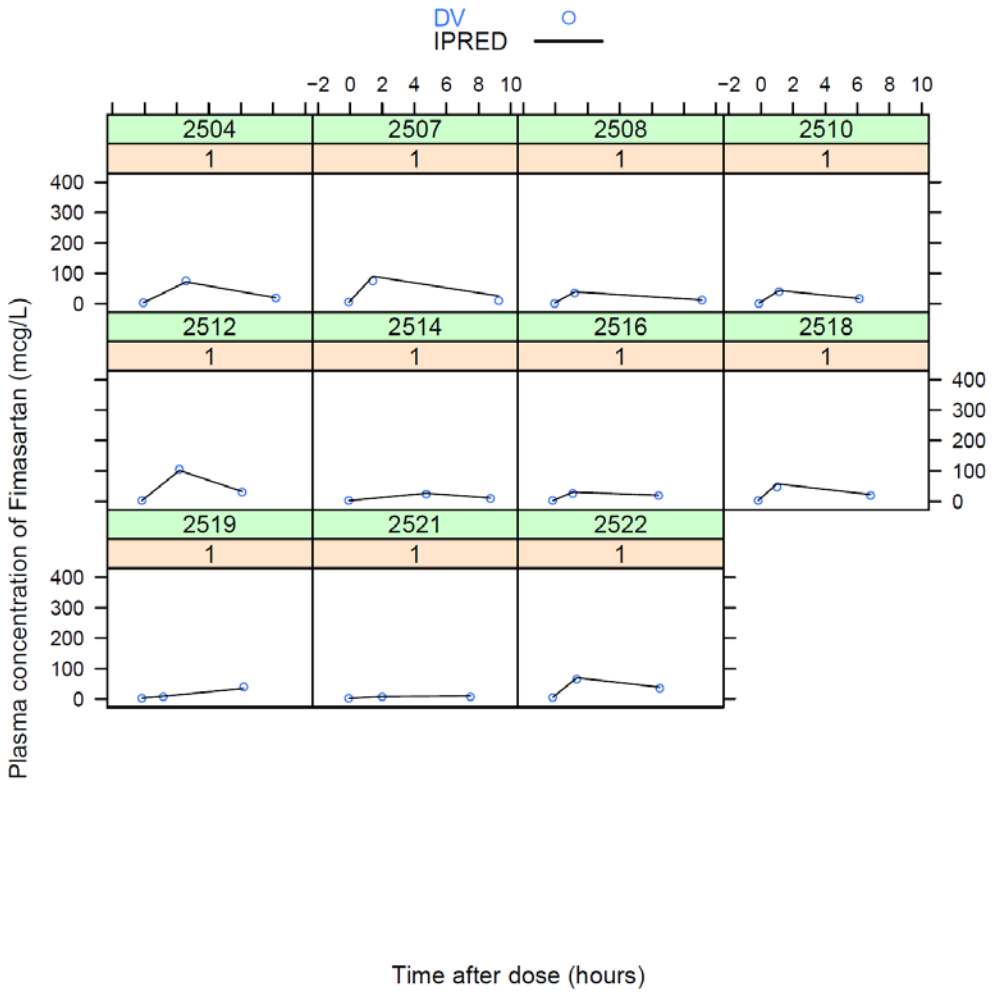
1: occasion period (1=period 1)



Individual fitting plot for the final pharmacokinetic model in study 4 (continuous)

Study 4 group: 2103, 2105, 2108, 2111, 2112, 2119, 2202, 2206, 2209, 2301, 2303, 2309, 2311, 2313, 2314, 2401, 2402, 2410, 2412, 2413, 2418, 2420, 2423, 2501, 2504, 2508, 2510, 2514, 2516, 2521 (60 mg), 2102, 2104, 2106, 2110, 2115, 2118, 2203, 2207, 2208, 2302, 2305, 2307, 2312, 2316, 2403, 2405, 2408, 2409, 2415, 2417, 2421, 2424, 2502, 2503, 2507, 2512, 2518, 2519, 2522 (120 mg)

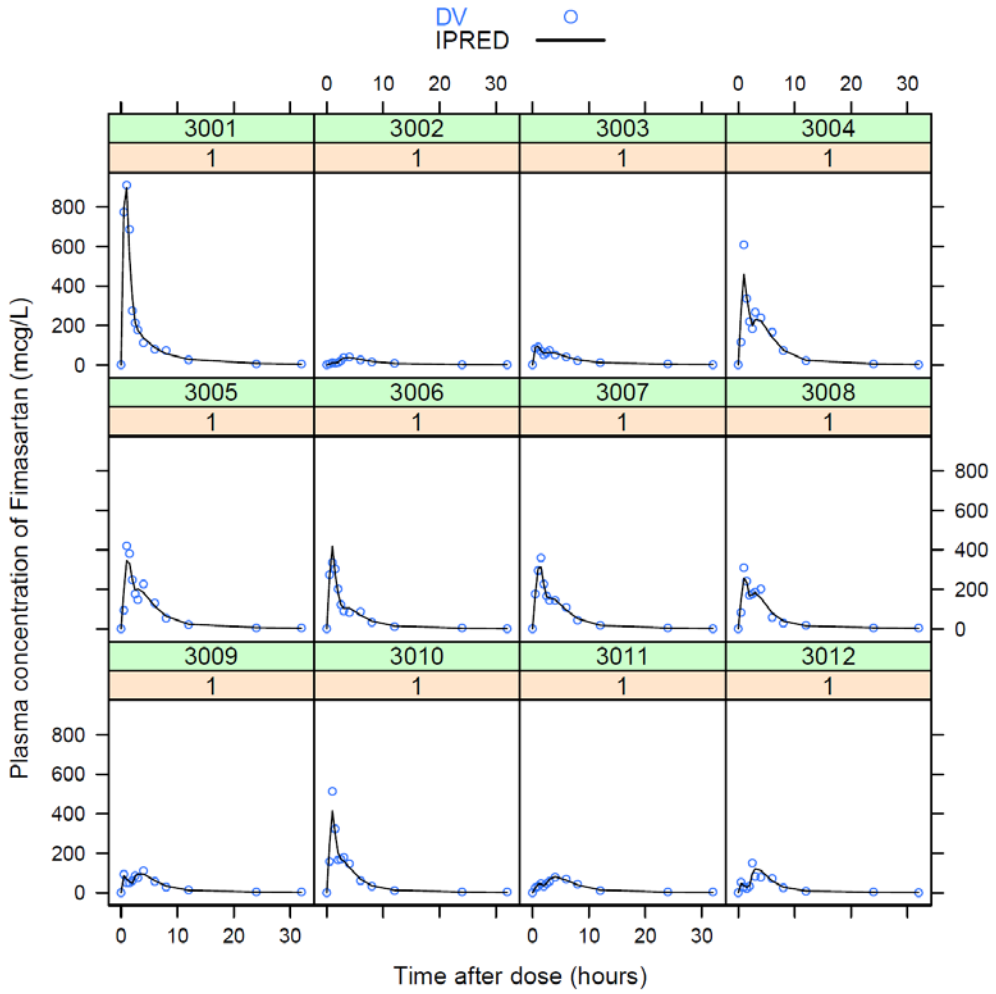
1: occasion period (1=period 1)



5. Individual fitting plot for the final pharmacokinetic model in study 5

Study 5 group: 3001-3024 (240 mg)

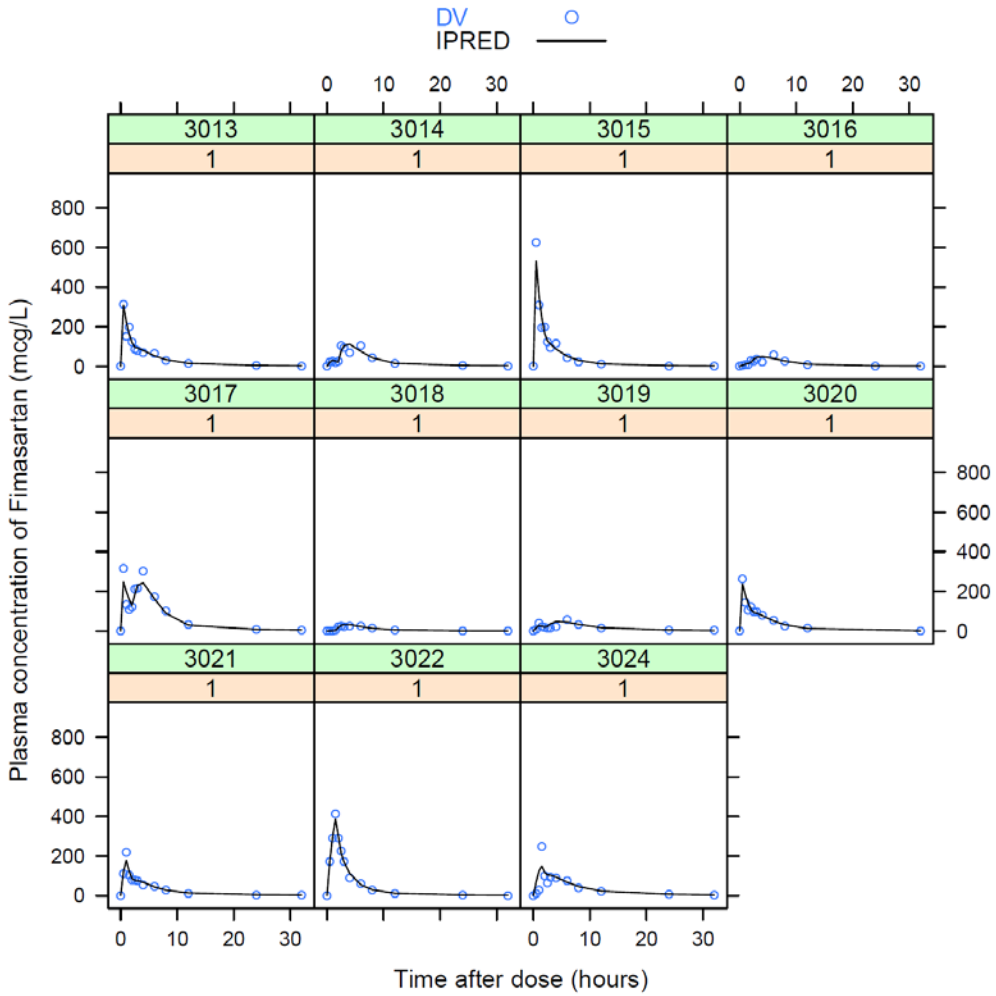
1: occasion period (1=period 1)



Individual fitting plot for the final pharmacokinetic model in study 5 (continuous)

Study 5 group: 3001-3024 (240 mg)

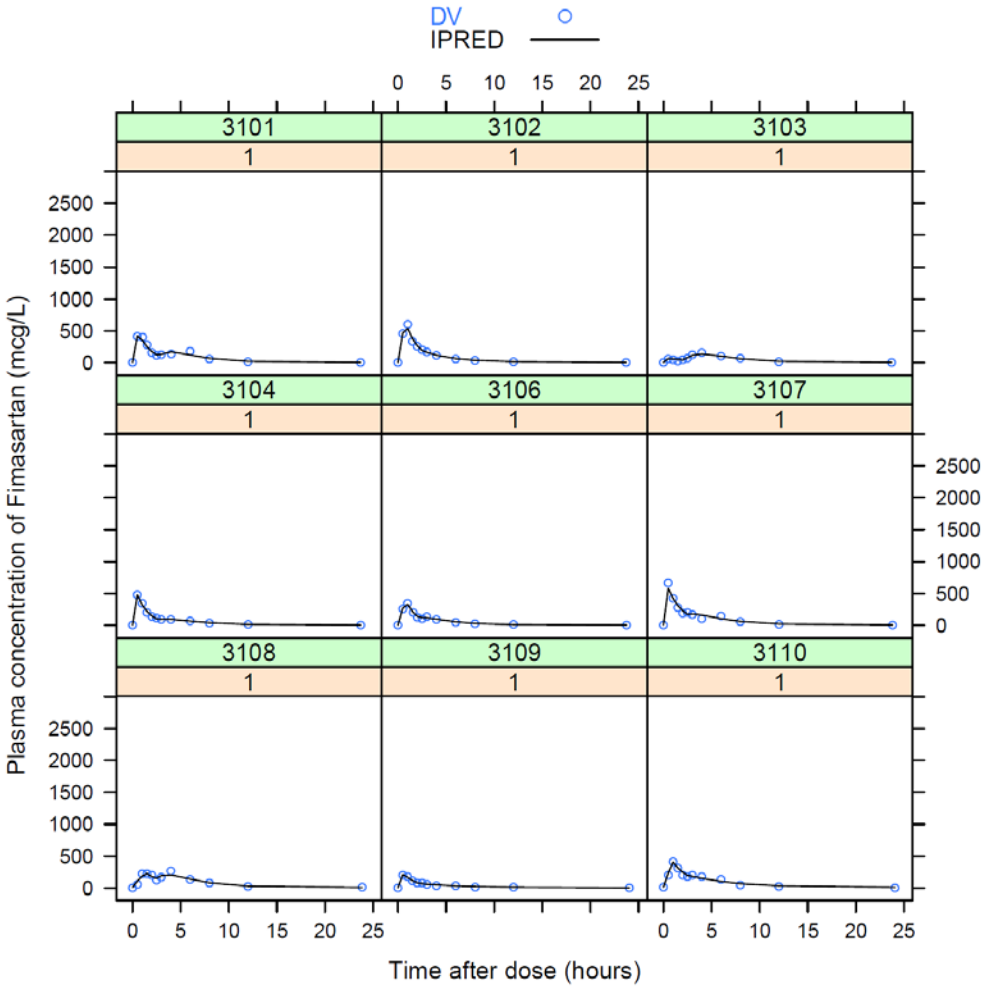
1: occasion period (1=period 1)



6. Individual fitting plot for the final pharmacokinetic model in study 6

Study 6 group: 3101-3120 (240 mg)

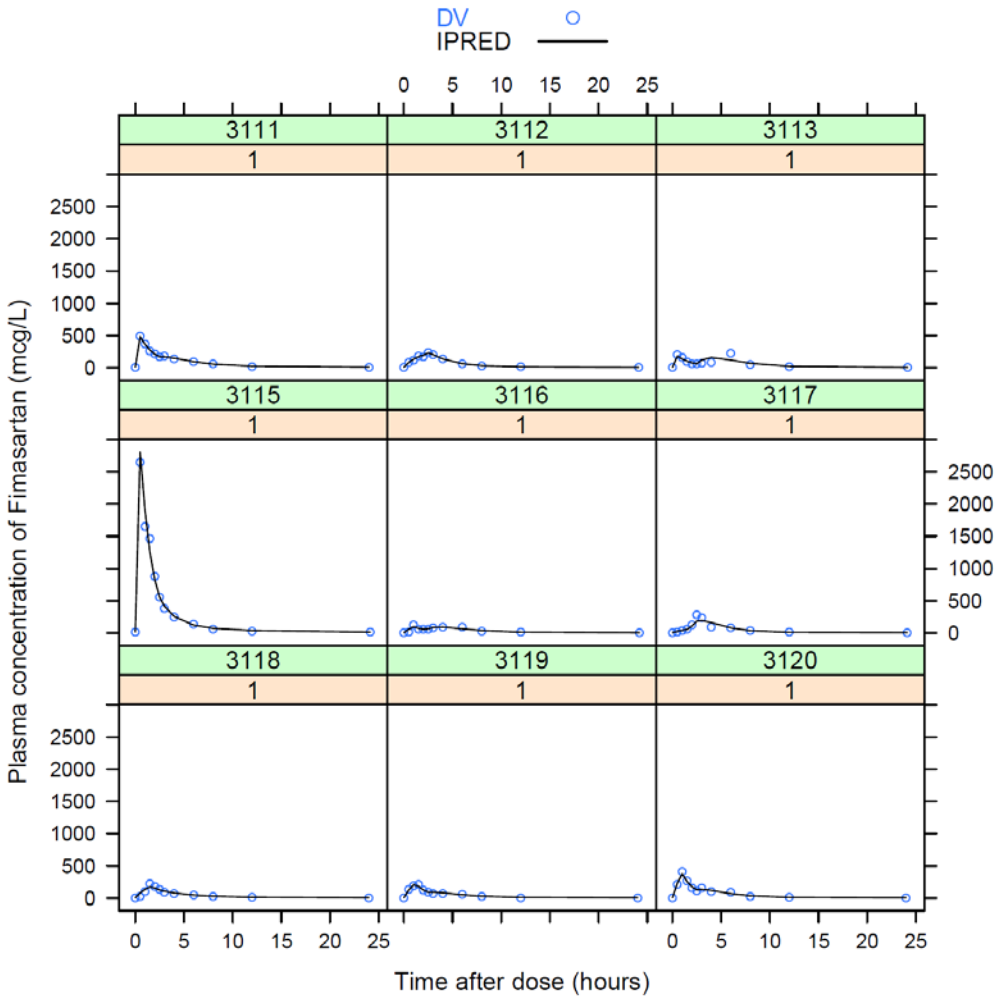
1: occasion period (1=period 1)



Individual fitting plot for the final pharmacokinetic model in study 6 (continuous)

Study 6 group: 3101-3120 (240 mg)

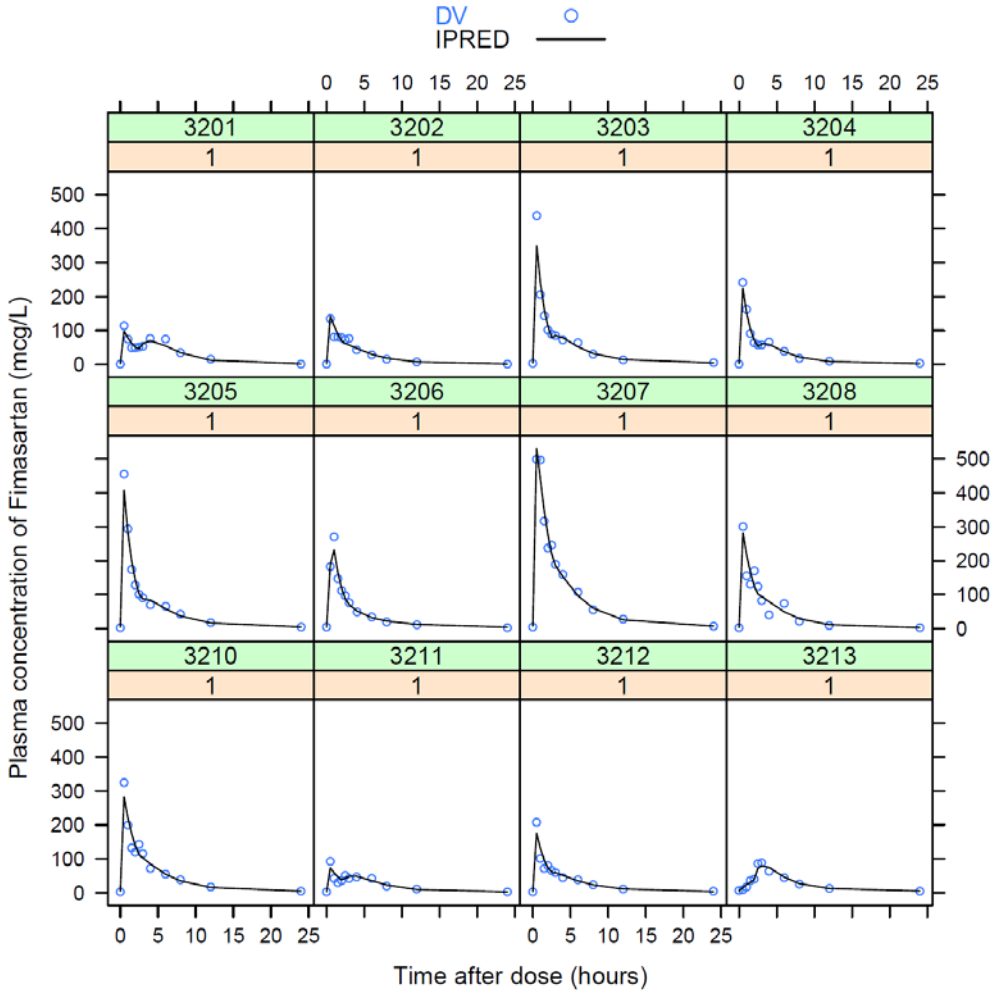
1: occasion period (1=period 1



7. Individual fitting plot for the final pharmacokinetic model in study 7

Study 7 group: 3201-3220 (120 mg)

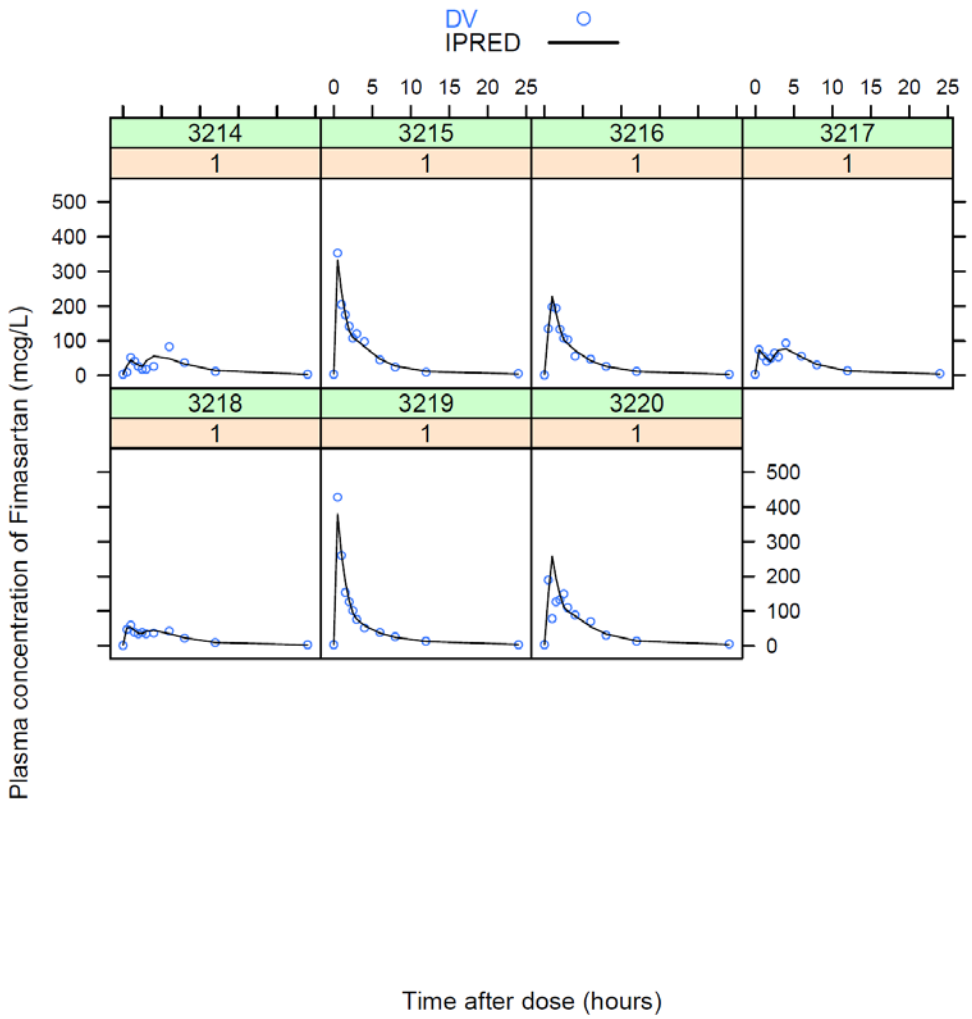
1: occasion period (1=period 1)



Individual fitting plot for the final pharmacokinetic model in study 7 (continuous)

Study 7 group: 3201-3220 (120 mg)

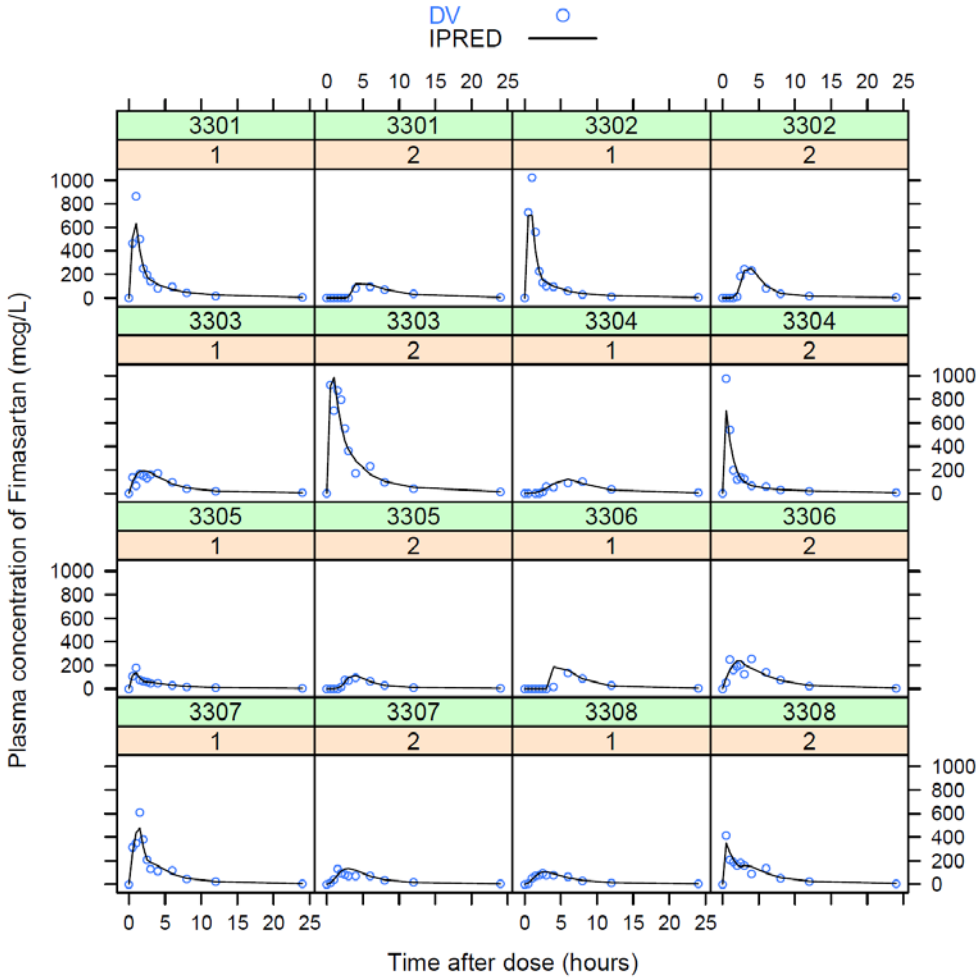
1: occasion period (1=period 1)



8. Individual fitting plot for the final pharmacokinetic model in study 8

Study 8 group: 3301-3324 (240 mg)

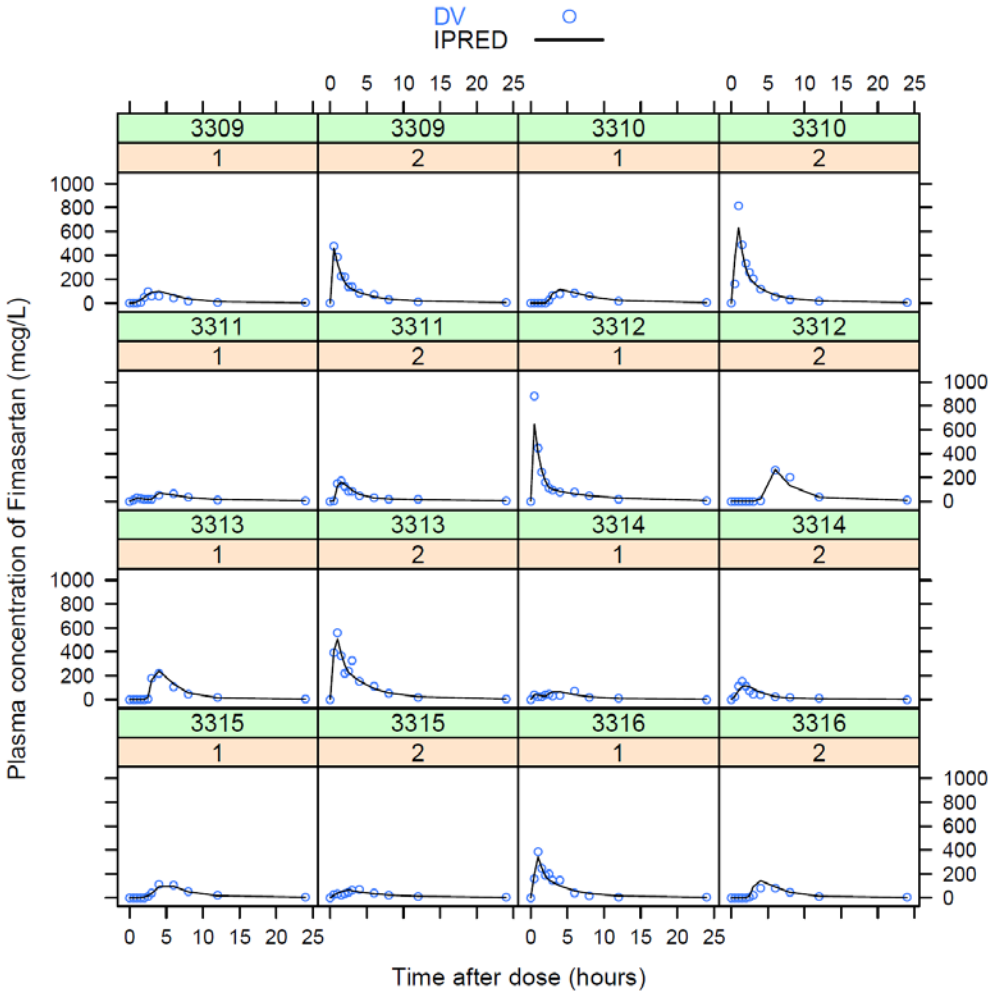
1, 2: occasion period (1=period 1, 2=period 2)



Individual fitting plot for the final pharmacokinetic model in study 8 (continuous)

Study 8 group: 3301-3324 (240 mg)

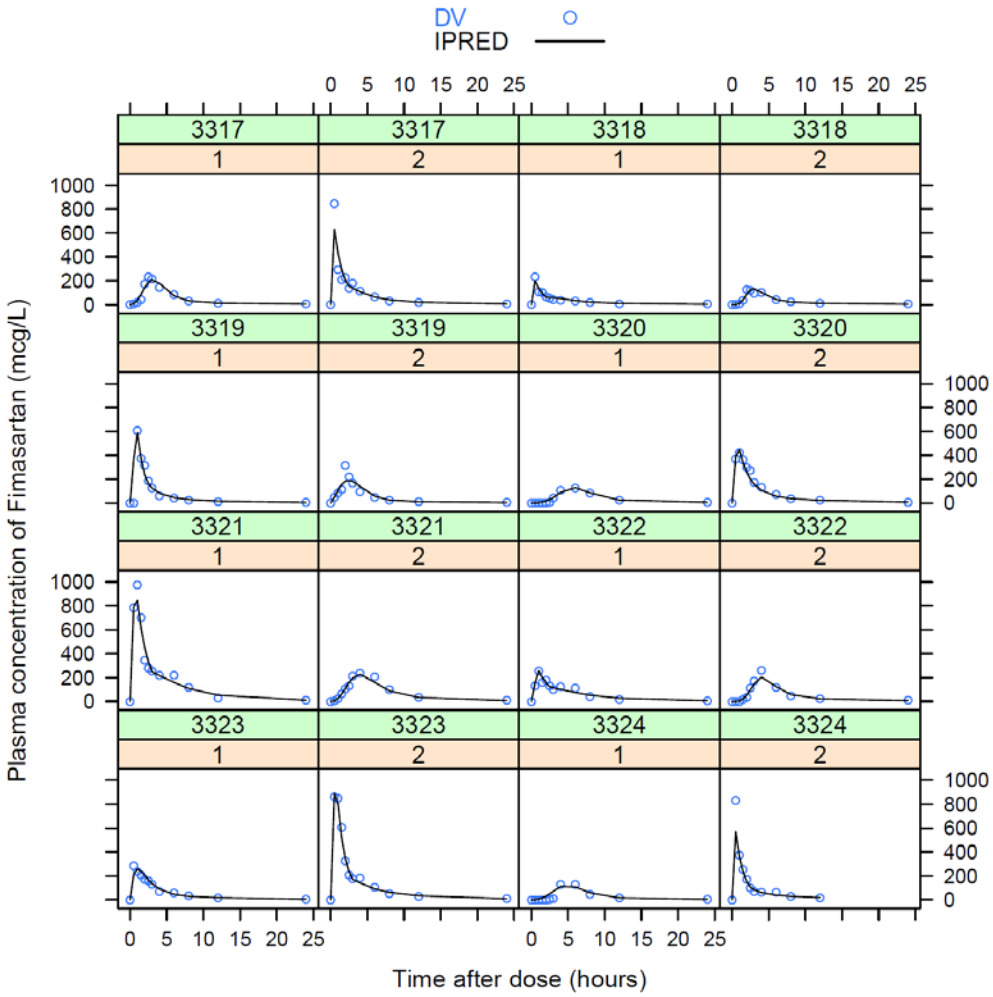
1, 2: occasion period (1=period 1, 2=period 2)



Individual fitting plot for the final pharmacokinetic model in study 8 (continuous)

Study 8 group: 3301-3324 (240 mg)

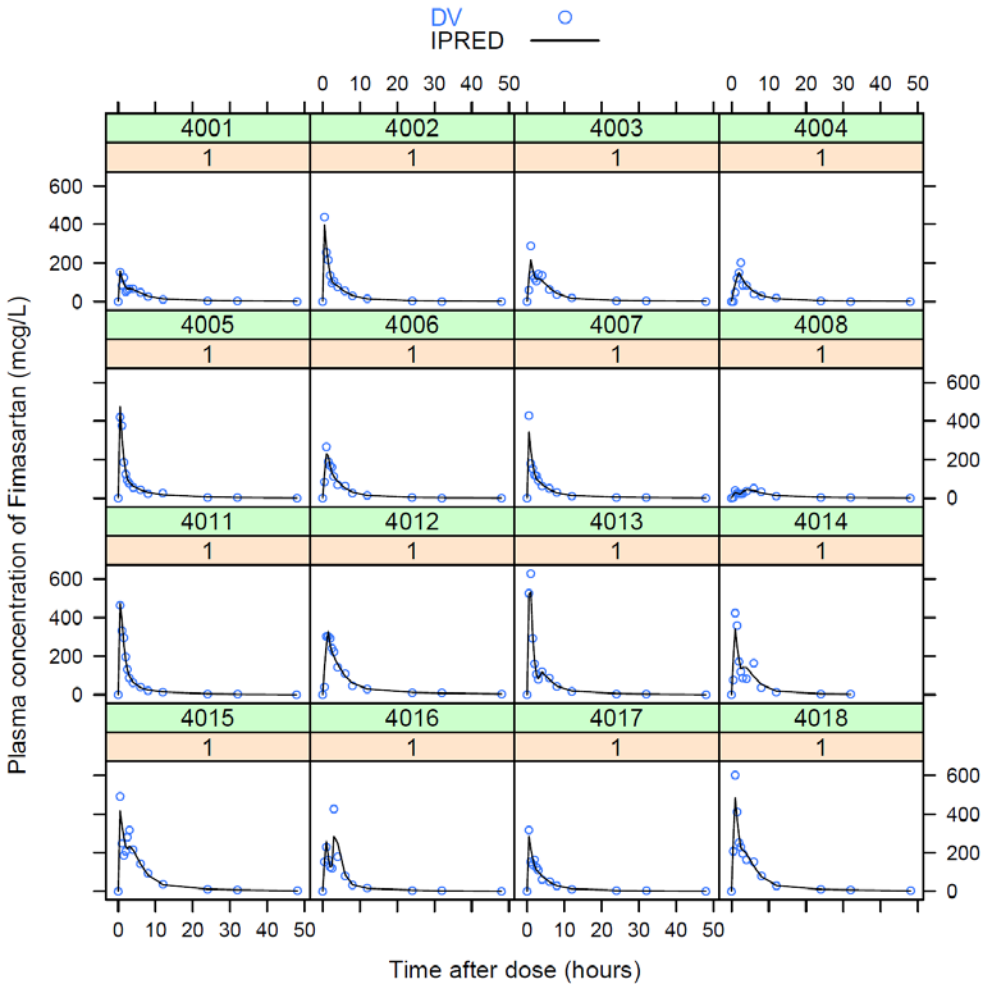
1, 2: occasion period (1=period 1, 2=period 2)



9. Individual fitting plot for the final pharmacokinetic model in study 9

Study 9 group: 4001-4008 (healthy subjects), 4011-4018 (severe renal impairment subjects)

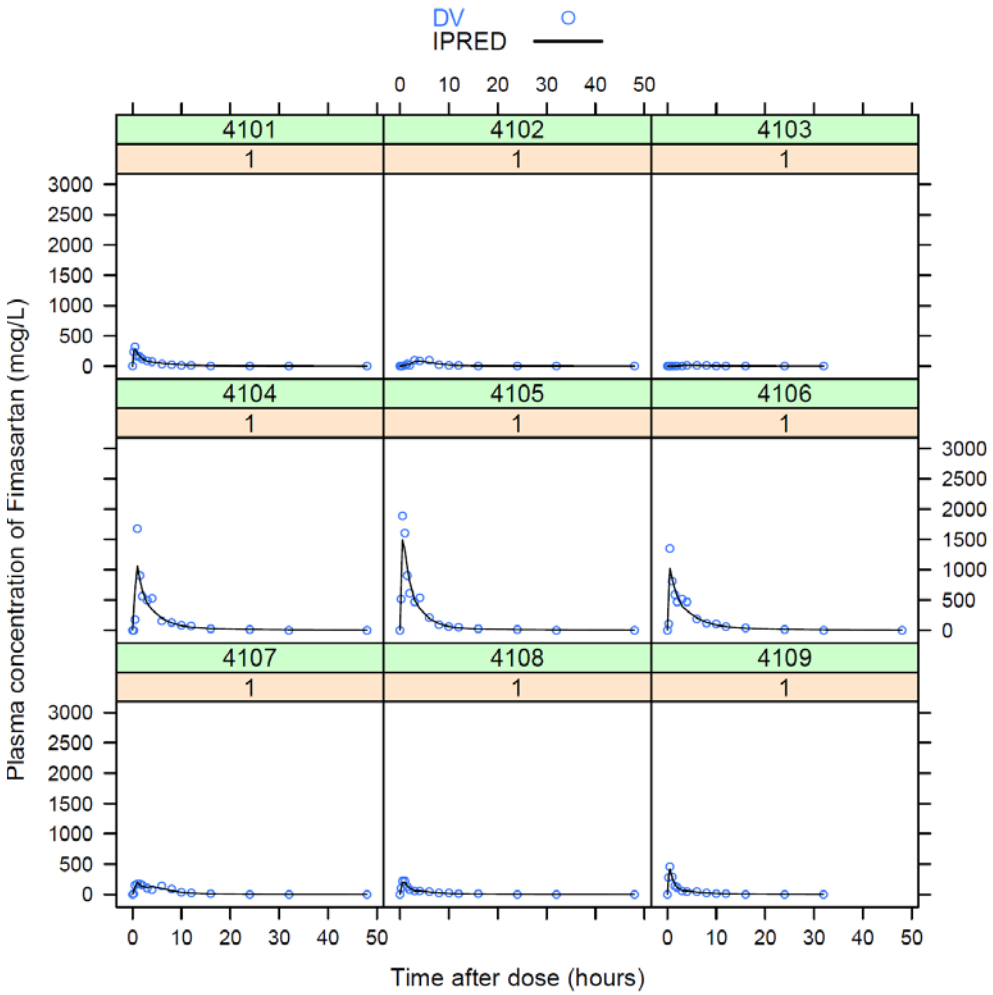
1: occasion period (1=period 1)



10. Individual fitting plot for the final pharmacokinetic model in study 10

Study 10 group: 4107, 4108, 4109, 4116, 4117, 4119 (healthy subjects), 4101, 4102, 4103, 4111, 4112, 4114 (mild hepatic impairment subjects), 4104, 4105, 4106, 4113, 4115, 4118 (moderate hepatic impairment subjects)

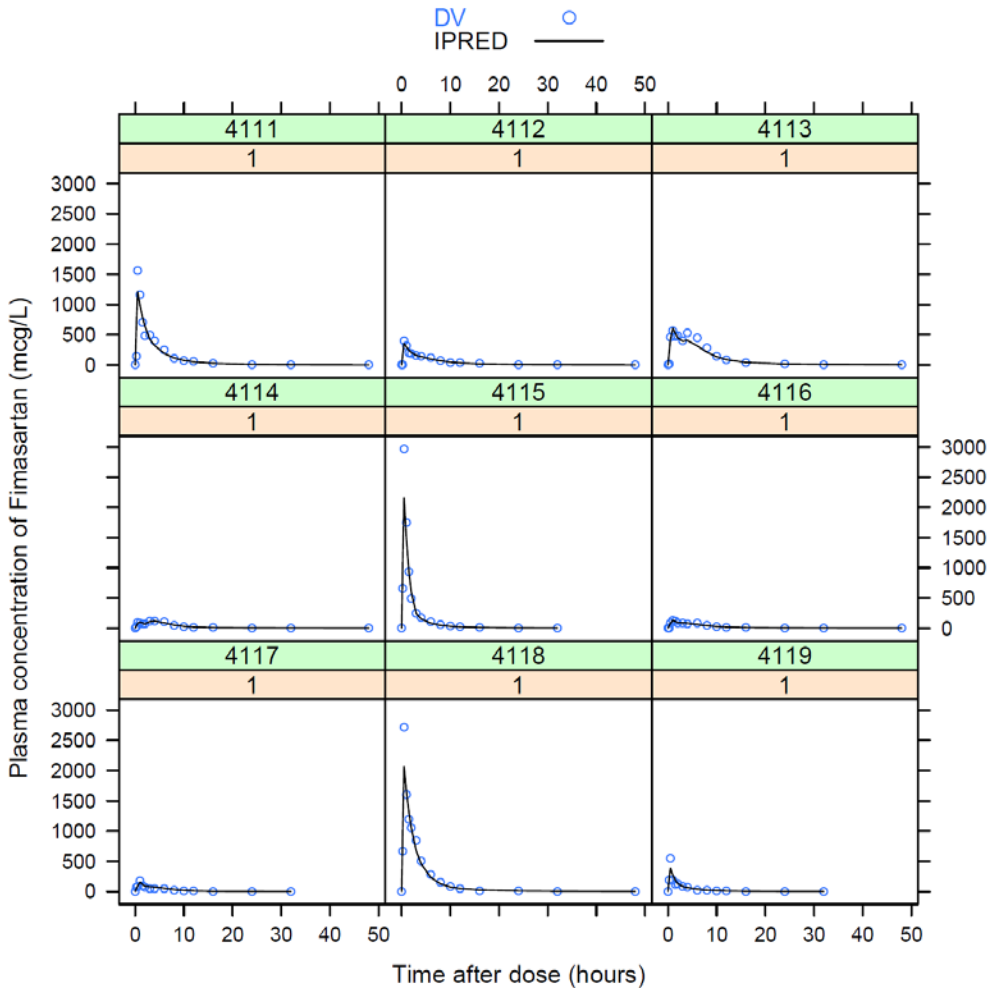
1: occasion period (1=period 1)



Individual fitting plot for the final pharmacokinetic model in study 10 (continuous)

Study 10 group: 4107, 4108, 4109, 4116, 4117, 4119 (healthy subjects), 4101, 4102, 4103, 4111, 4112, 4114 (mild hepatic impairment subjects), 4104, 4105, 4106, 4113, 4115, 4118 (moderate hepatic impairment subjects)

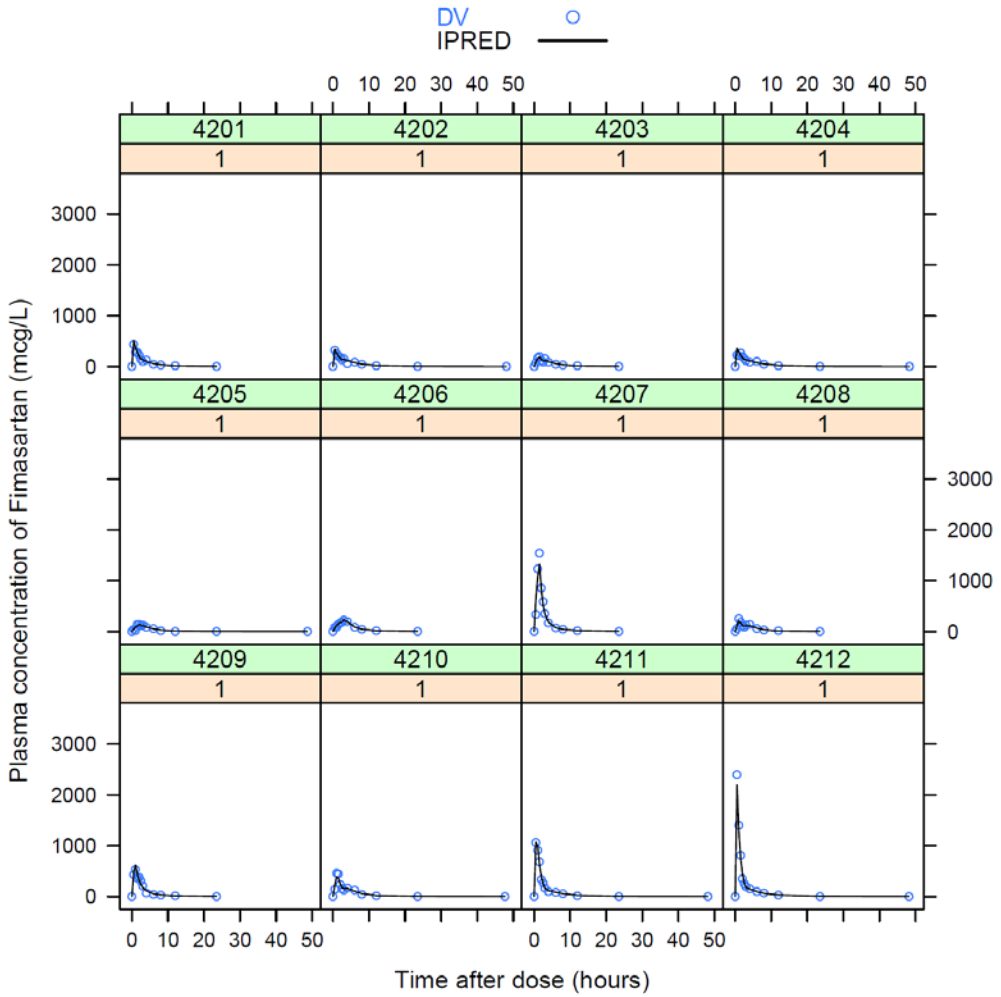
1: occasion period (1=period 1)



11. Individual fitting plot for the final pharmacokinetic model in study 11

Study 11 group: 4201-4212 (young subjects), 4213-4222 (elderly subjects)

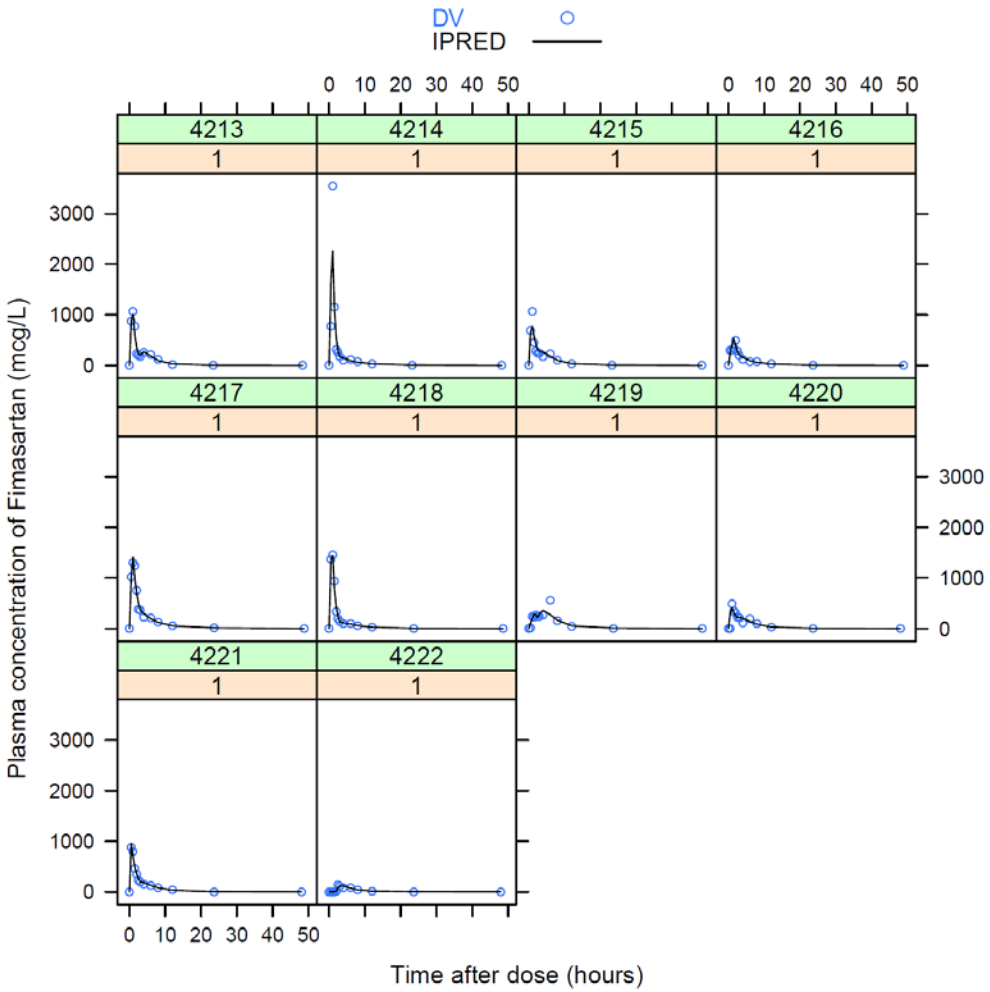
1: occasion period (1=period 1)



Individual fitting plot for the final pharmacokinetic model in study 11 (continuous)

Study 11 group: 4201-4212 (young subjects), 4213-4222 (elderly subjects)

1: occasion period (1=period 1)



Abstract in Korean

건강 자원자와 고혈압 환자에서 fimasartan의 집단 약동학 연구

서론: Fimasartan은 안지오텐신 II 수용체 type 1을 선택적으로 차단하여 혈압을 조절하는 새롭게 개발된 항고혈압 약물이다. 본 연구에서는 건강 자원자와 고혈압 환자의 임상시험 자료를 활용하여 fimasartan의 집단약동학 모델을 개발하고 의미 있는 공변량을 찾는 것이다.

방법: 본 연구에서 사용한 임상시험 자료는 건강한 사람을 대상으로 하는 제 1상 임상시험(first-in-human study), 용량-반응에 대한 개념입증 임상시험(proof-of-concept dose-response study), 약물 상호작용 임상시험(Drug interaction study), 음식물 영향 임상시험, 특수환자에서 임상시험 (간장애 환자, 신장애 환자, 노인)을 포함하였다. 11개의 임상시험에 참여한 시험대상자 268명의 혈중 농도 및 채혈시간 자료를 활용하였으며, NONMEM(ver. 7.40) 소프트웨어의 비선형혼합효과 모형을 사

용하여 fimasartan의 집단 약동학 모델을 구축하였다. 개발한 모델의 타당성을 검증하기 위하여 적합도 플롯(goodness of fit plot)와 시각적 예측 확인(visual predictive check)을 사용하였다.

결과: Fimasartan의 집단약동학 모델은 혼합 흡수 (0차 흡수와 1차흡수), 지연시간 및 1차 소실을 따르는 2구획 모델이 선정되었으며, 개인간 변이를 추정하기 위하여 비례 오차 모델이 선택되었다. 본 모델을 통하여 얻은 겉보기 청소율, 겉보기 분포용적, 1차 속도로 흡수되는 비율의 집단 추정값(개체간 변이, CV%)은 각각 159L/h(53.7%), 371L(71.8%), 0.367(114.6%)이었다. 몸무게 및 연령이 집단약동학 모델의 공변량으로 선택되었다. 개발된 fimasartan 집단약동학 모델의 타당함을 적합도 플롯(goodness of fit plot), 시각적 예측 확인(visual predictive check)을 통해 검증하였다.

결론: 본 연구에서는 다양한 연구에서 얻어진 fimasartan의 혈중농도를 이용하여 fimasartan의 집단약동학 모델을 개발하였다. 몸무게와 간기능 상태가 fimasartan의 집단약동학 모델의 중요한 공변량임을 밝혔다.

중심단어: 집단약동학 모델; NONMEM; 공변량; Fimasartan

학번: 2015-26111